PROCRIT®: Clinical Study Report PR00-06-014 (CHOIR)

SYNOPSIS

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: N/A	N/A
NAME OF ACTIVE INGREDIENT(S): epoetin alfa; recombinant human erythropoietin	Page: N/A	

Protocol No.: PR00-06-014

Title of Study: Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR)

Study Principal Investigators: Donal Reddan, MB, MHS, MRCPI – Galway Clinic, Galway, Ireland; Ajay K. Singh, MD, MBA – Brigham and Women's Hospital and Harvard Medical School, Cambridge, MA

Publication (Reference):

Tran LL, et al. Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR): Study Design. Am J Kid Dis. 2002;39(4):A27. Abstract 67.

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Singh A, et al. Factors Associated with Hemoglobin (Hb) Response in Patients (PTS) with Anemia of Chronic Kidney Disease (CKD). J Am Soc Nephrol. 2003;14:457A. Abstract SA-PO726.

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Singh A, Reddan D. Can Risk Factor Modification Provide Meaningful Benefit? The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Study. J Am Soc Nephrol. 2003;14:809A. Abstract PUB170.

Singh A, et al. Medication Use Among CKD Patients: An Analysis of Baseline Data from the CHOIR Study. Am J Kid Dis. 2004;43(4):A41. Abstract 107.

Singh A, et al. Iron Deficiency in CKD Patients: Baseline Data from the CHOIR Study. J Am Soc Nephrol. 2004;15:585A. Abstract SU-PO240.

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Reddan D, et al. Prior Cardiovascular Events Among CKD Subjects with Anemia: Baseline Data from the CHOIR Study. J Am Soc Nephrol. 2004;15:131A. Abstract F-PO299.

Singh A, et al. Medication Use Among CKD Patients with Cardiac Disease: Baseline Data from the CHOIR Study. J Am Soc Nephrol. 2004;15:799A. Abstract PUB173.

Study Initiation/Completion Dates: April 17, 2002/August 23, 2005	**Phase of development:** IV

Objective: The primary objective of this study was to compare the composite cardiovascular event rates for chronic kidney disease (CKD) patients randomized to a target hemoglobin (Hb) level of 13.5 g/dL (Group A: high Hb arm) versus a target Hb level of 11.3 g/dL (Group B: low Hb arm) over a 3-year study period. A composite event was defined as follows: all-cause mortality, congestive heart failure (CHF) hospitalization where renal replacement therapy (RRT) did not occur, non-fatal myocardial infarction (MI), or non-fatal stroke.

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Methodology: This was a prospective, randomized, open-label, multi-center study in patients with CKD not on dialysis. Patients were randomized into 2 treatment groups. For Group A, therapy was directed at maintaining the Hb level as close to 13.5 g/dL as possible, and for Group B, therapy was directed at maintaining the Hb level as close to 11.3 g/dL as possible. Patients were to be followed every other week until the Hb stabilized and then monthly for up to 3 years or until initiation of RRT. Serious adverse events (SAEs) were to be reported up to 90 days following completion or early withdrawal. All potential composite events (except for death) were adjudicated by a clinical event classification committee (CEC), which was blinded to treatment group. A data safety monitoring board (DSMB) reviewed all safety data on an ongoing basis and was to review the results of 4 pre-specified interim analyses for safety and efficacy.

Number of Patients (planned and analyzed): Enrollment was planned to be a total of 1352 patients. There were 1432 patients randomized and analyzed: 715 in the 13.5 g/dL Hb group and 717 in the 11.3 g/dL Hb group. All randomized patients were included in the intention-to-treat (ITT) population and 1421 patients who received at least one dose of PROCRIT® were included in the safety population. A total of 1395 patients who were treated according to the randomized treatment assignment, met all inclusion/exclusion criteria, received at least one dose of study medication, and had at least one post-randomization Hb measurement were included in the per-protocol population.

Diagnosis and Main Criteria for Inclusion: Adult patients with CKD not on dialysis and with an entry Hb <11 g/dL and glomerular filtration rate (GFR) of $\geq$15 mL/min/1.73m^2 and $\leq$50 mL/min/1.73m^2 were included in this study. Female patients could not be pregnant or lactating.

Test Product, Dose and Mode of Administration, Batch No.: PROCRIT® was administered by subcutaneous (SC) injection. The starting dose of PROCRIT® for all eligible patients was 10,000 units subcutaneously once a week. After the initial 3 weekly doses, subsequent doses and dosing intervals of PROCRIT® were adjusted based on an assessment of the 2 most recent Hb values. Investigators used algorithms to determine the required dose. The maximum dose permitted was 20,000 units. Once a patient reached the target Hb and remained stable at that level, the weekly dosing schedule was modified to give twice the current dose every other week, up to a maximum of 20,000 units. Batch numbers used were: P001310, P002176, P002414, P003497, P003498, P005262, P006212, P007982, P008400, P008873, P008954, P009114, P009115, P009413, P009677, P010982, P010983, P011375, P011376, P024755, P024844, P024845, P024894, P027186, P028154, P029309, P029325, P031221, P031222, and P032913.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable. All patients received PROCRIT®.

Duration of Treatment: Patients were to receive PROCRIT® up to the point of initiation of RRT or for a maximum of 36 months.

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Criteria for Evaluation:

Efficacy:

The primary outcome was a composite consisting of all-cause mortality, CHF hospitalization (not including hospitalizations during which RRT occurred), non-fatal MI, and non-fatal stroke.

The secondary outcomes included the following:

- All-cause mortality
- CHF hospitalization (where RRT did not occur)
- Non-fatal MI
- Non-fatal stroke
- RRT and RRT hospitalization
- Cardiovascular hospitalizations (including hospitalizations for CHF, stroke, MI, acute coronary syndromes, cardiac interventions, peripheral vascular disease procedures, and vascular access procedures)
- All-cause hospitalizations
- Hospitalizations for vascular access (for dialysis) procedures and proteinuria
- Changes from baseline in Hb/hematocrit (Hct), PROCRIT® dose, iron stores, kidney disease status including GFR, nutritional status, development of incident CHF (determined using National Health and Nutrition Examination Survey [NHANES] I criteria), health-related quality of life and functional status, and comorbid conditions

Safety: Safety evaluations included adverse events (AEs), SAEs, laboratory tests, blood pressure, heart rate, baseline electrocardiograms (ECGs), physical examination findings, and anti-erythropoietin antibody testing.

SYNOPSIS (CONTINUED)

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Statistical Methods: The primary efficacy analysis compared the 2 treatment groups on the composite of all-cause mortality, CHF hospitalization (where RRT did not occur), non-fatal MI, or non-fatal stroke occurring between randomization and termination, defined as study completion or early withdrawal. The analysis compared the time to the first event between the 2 treatment groups using Kaplan-Meier survival analysis and the log-rank test. The analysis of the primary outcome was conducted using the ITT population. The primary outcome was also analyzed using the per-protocol population.

In addition, 3 sensitivity analyses, using both ITT and per-protocol populations, were conducted to evaluate (1) composite events occurring from randomization up to termination or 30 days post study medication (whichever occurred later), (2) composite events occurring from randomization through, 90 days post termination or last reported event, and (3) composite events occurring between the first dose of study medication and 30 days post study medication.

The Cox proportional hazard model was used to further evaluate and compare the composite events between the 2 groups. Possible covariates of outcome included demographic variables such as gender, race, and age and baseline clinical variables such as renal history, NHANES scores, diabetes mellitus status, GFR, albumin, reticulocyte count, and iron status. These variables were evaluated in the multivariate Cox proportional hazard model using a stepwise variable selection procedure. The variables that were statistically significant at the 0.05 level from the stepwise procedure were further evaluated using the best subset selection method. The criterion used to select the best subset was based on the global score chi-square statistic.

The time to each type of event included in the list of secondary outcomes was also compared between groups using Kaplan-Meier survival analysis and the log-rank test.

Last values for Hb, Hct, iron parameters, kidney disease status, nutritional status, NHANES scores, and quality-of-life (QOL) scores were compared between groups using analyses of covariance (ANCOVA) with baseline scores as covariates. Repeated-measures analysis of variance (ANOVA) was used to compare parameter values over time between the 2 groups. Time to Hb response was estimated using Kaplan-Meier methods and compared between groups using the log-rank test. The percentage of patients in each GFR category at baseline and the end of the study was compared between groups using the Cochran-Mantel-Haenszel test. The percentage of patients with NHANES scores <3 or ≥3 were compared between groups using chi square tests. The percentages of patients with transfusions were compared between groups using Fisher's exact test. Kaplan-Meier methods and the log-rank test were used to compare time to first transfusion during the study between the two treatment groups.

Adverse events, SAEs, baseline ECG parameters, and physical examination results were summarized descriptively using the safety population. Changes from baseline to final value for safety laboratory tests and vital signs were compared between groups using ANCOVA with baseline scores as covariates.

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SUMMARY - CONCLUSIONS

<u>EFFICACY RESULTS</u>:

Interim Analysis Results

The first interim analysis was conducted in December 2003 after 37 composite events had occurred (17 in Group A and 20 in Group B). The DSMB recommended that the study continue.

A second interim analysis was conducted in May 2005 after 145 composite events had occurred (80 in Group A and 65 in Group B). The hazard ratio of the likelihood of the occurrence of the composite event was 1.264 (95% confidence interval [CI]: 0.911 to 1.753) in Group A (the high Hb group) compared with Group B (the low Hb group). The estimated conditional power to demonstrate the reduction of the composite event rate for the high Hb group over the low Hb group, should the study be completed as originally planned, was less than 5%. Based on these results, the DSMB recommended termination of the study. The study was stopped on May 26, 2005.

Final Analysis Results

Primary Outcome

In the ITT population, there were 125 patients [17.5%] in Group A (the high Hb group) and 97 patients [13.5%] in Group B (the low Hb group) who experienced a composite event between randomization and study termination. The event rates over time for the two treatment groups were statistically significantly different (P=0.0312, log-rank test). The hazard ratio for experiencing a composite event between randomization and termination for the high Hb group versus the low Hb group was 1.337 (95% confidence interval [CI]: 1.025 to 1.743), indicating that a patient in Group A was 1.337 times as likely to experience a composite event as a patient in Group B. Among the 222 patients who experienced a composite event, there were:

- 65 (29.3%) deaths, 39 (31.2%) in Group A and 26 (26.8%) in Group B;

- 101 (45.5%) CHF hospitalizations (where RRT did not occur), 59 (47.2%) in Group A and 42 (43.3%) in Group B;

- 25 (11.3%) non-fatal MIs, 12 (9.6%) in Group A and 13 (13.4%) in Group B;

- 23 (10.4%) non-fatal strokes, 12 (9.6%) in Group A and 11 (11.4%) in Group B;

- 0 event of stroke and death in Group A and 1(1%) in Group B;

- 7 (3.2%) events of CHF hospitalization (without RRT) and non-fatal MI, 3 (2.4%) in Group A and 4 (4.1%) in Group B

These are described in Table 5-3. Death and CHF hospitalizations (without RRT) accounted for 74.8% of the composite events. The results of the per-protocol population were consistent with the ITT population. Results from the additional sensitivity analyses were also consistent with those from the primary analysis.

The results of the multivariate analyses suggested that pre-existing medical conditions of CHF, NHANES CHF score ≥3, and atrial fibrillation/flutter; baseline laboratory values of lower serum albumin and higher percent reticulocyte count; and older age were significantly associated with the occurrence of composite events. When these baseline variables were included in the multivariate analyses, the association between randomization group and composite event was no longer statistically significant. However, a trend toward a higher risk of events in Group A remained (hazard ratio 1.243 [95% CI: 0.951 to 1.624], P=0.111).

These data suggest that baseline patient factors are important in predicting composite events.

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Secondary Outcomes

Results for other clinically significant events:

- All-cause mortality: Group A, 52 (7.3%); Group B, 36 (5.0%); *P*=0.0674
- CHF hospitalization (where RRT did not occur): Group A, 64(9.0%); Group B, 47 (6.6%); *P*=0.0727
- Non-fatal MI: Group A, 18 (2.5%); Group B, 20 (2.8%); *P*=0.7836
- Non-fatal stroke: Group A, 12 (1.7%); Group B, 12 (1.7%); *P*=0.9803
- RRT: Group A, 155 (21.7%); Group B, 134 (18.7%); *P*=0.1467
- RRT hospitalization: Group A, 99 (13.8%); Group B, 81 (11.3%); *P*=0.1320
- Cardiovascular hospitalization: Group A, 233 (32.6%); Group B, 197 (27.5%); *P*=0.0350
- All-cause hospitalization: Group A, 369 (51.6%); Group B, 334 (46.6%); *P*=0.0284
- Hospitalization for vascular access: Group A, 73 (10.2%), Group B, 57 (7.9%); *P*=0.1213
- Hospitalization for proteinuria: Group A, 25 (3.5%); Group B, 14 (2.0%); *P*=0.0703

Results for other planned analyses:

- All CHF hospitalization (including those where RRT occurred): Group A, 79 (11.0%); Group B, 57 (7.9%); *P*=0.0366
- Composite of death, MI, stroke, or CHF hospitalization (including hospitalizations where RRT occurred): Group A, 137 (19.2%); Group B, 104 (14.5%); *P*=0.0157
- Composite event or RRT: Group A, 256 (35.8%); Group B, 208 (29.0%); *P*=0.0075

Results for Hb response:

There were significant increases in Hb levels over time in both groups. The final Hb value for Group A was 12.6 g/dL, a 2.5 g/dL increase from baseline, and for Group B it was 11.3 g/dL, a 1.2 g/dL increase from baseline (*P*<0.001). For Group A, 75.9% of patients reached the target Hb (13.5 g/dL). For Group B, 93.9% of patients reached the target Hb (11.3 g/dL). The time to reach the target Hb was longer for patients in Group A than for patients in Group B (*P*<0.0001). In both groups, 95.2% of patients achieved ≥1.0 g/dL increase in Hb from baseline.

Results for iron status:

There was a decline in iron stores at Month 3 in both groups. The decline was much greater in Group A compared with Group B. In general, for the duration of the study, iron stores increased towards baseline from their lowest value at Month 3, suggesting that patients received supplemental iron, as dictated by the protocol. This is supported by the increase in the proportion of patients treated with iron supplementation during the study (50.1%), as compared with the proportion of patients treated with iron in the 3 months prior to randomization (30.0%). After Month 3, the iron stores in Group A were maintained nearer to baseline than in Group B, despite the fact that significantly higher PROCRIT® doses were administered to Group A patients. These findings, taken together, suggest that patients in Group A received more iron supplementation than those in Group B.

Results for kidney disease status:

Glomerular filtration rate declined during the study in both groups. The mean decline at last value was slightly greater in Group A (-3.6 mL/min/1.73 m^2) compared with Group B (-2.7 mL/min/1.73 m^2); *P*=0.050. Changes in creatinine clearance and serum creatinine were not different between the two groups.

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Results for nutrition status:

Serum albumin decreased slightly in both groups (mean -0.1 g/dL at last value) over the duration of the study, and there were no significant differences in albumin change from baseline at the final value, although there was a trend for higher serum albumin at final value in Group B (3.8 g/dL) compared with Group A (3.7 g/dL) (P=0.076).

Results for NHANES CHF score:

More patients in Group A had NHANES CHF score ≥3 compared with Group B at baseline (26.6% vs. 21.1%, P=0.016). While the difference was not statistically significant, there remained a trend toward a higher proportion of patients with NHANES CHF score ≥3 in Group A at last value compared with Group B (22.4% vs. 17.9%, P=0.066). It should be noted that NHANES CHF scores were collected annually and there were many missing values.

Results for quality of life:

Quality-of-life parameters (Short Form [SF]-36, Linear Analog Scale Assessment [LASA], and Kidney Disease Questionnaire [KDQoL]) significantly improved in both patient groups from baseline to the end of the study; however, there were no between-group differences except in the role-emotional scale from the SF-36, which was in favor of Group B (P=0.011).

SAFETY RESULTS:

Overall, 87.0% of patients in the safety population experienced at least one adverse event during the study. The incidence of AEs overall and of each individual AE was very similar in Groups A and B. Patients reported AEs most frequently in the following system organ classes: infections and infestations (49.6%), gastrointestinal disorders (36.0%), general disorders and administration-site conditions (34.5%), musculoskeletal and connective tissue disorders (34.4%), and metabolism and nutrition disorders (33.5%). The most frequently reported individual AEs were hypertension (15.4%), peripheral edema (13.3%), nausea (12.4%), nasopharyngitis (12.3%), urinary tract infection (11.2%), diarrhea (11.1%), congestive cardiac failure (10.6%), and upper respiratory tract infection (10.2%). Chronic kidney disease is associated with a high adverse event rate, and the events reported during this study were consistent with events commonly reported in patients with chronic kidney disease.

Severe AEs were more common overall in Group A than in Group B, particularly cardiac disorders (12.39% vs. 9.73%) and renal and urinary disorders (12.39% vs. 8.86%).

The majority of patients experienced only AEs that were considered not related to study drug. There were no notable differences between groups in AEs by relationship to study drug.

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Death is not uncommon in patients with chronic kidney disease, and causes of death in this study reflected the usual causes of death in the chronic kidney disease patient population. The most frequent causes of deaths were cardiac arrest, acute MI, sepsis or infection, stroke, renal disease, and other non-cardiovascular causes. Death from stroke was similarly frequent between the two groups (5 patients in each group) and MI was slightly more frequent in Group B (10 patients vs. 6 patients in Group A). Death from CHF was more frequent in Group A (6 patients vs. 1 in Group B). Death from cardiac arrest was more frequent in Group A (12 patients vs. 6 patients in Group B), while death from coronary artery disease occurred only among patients in Group B (6 patients). Death from sepsis or infection was also more frequent in Group A (10 patients) compared with Group B (1 patient).

Overall, 51.7% of patients in the safety population experienced at least one SAE during the study. The incidence of SAEs overall and of each individual SAE was very similar in the high and low Hb groups, except that congestive heart failure was slightly more frequent in the high Hb group (11.2% of patients vs. 7.4% in the low Hb group). The most frequently reported SAEs were congestive heart failure (9.3% of patients overall), chronic renal failure (6.4%), acute renal failure (4.8%), pneumonia (4.4%), chest pain (2.8%), gastrointestinal hemorrhage (2.6%), myocardial infarction (2.1%), and cellulitis (2.0%).

Thirteen patients had a total of 14 SAEs that were considered possibly or probably related to study drug, including 10 patients (11 SAEs) in Group A and 3 patients (3 SAEs) in Group B. The related SAEs included 2 pulmonary emboli (1 in Group A and 1 in Group B), 3 SAEs of deep vein thrombosis (all in Group A), and one SAE each of the following: retinal vein occlusion, transient ischemic attack, hypertension, priapism, rash, allergic dermatitis, cerebrovascular accident, and unstable angina.

Thrombotic vascular events (TVEs) were reported in 126 patients (18.4%) in Group A and 120 (17.4%) in Group B. Clinically relevant TVEs (defined as myocardial infarction, cerebrovascular accident, angina pectoris, transient ischemic attack, and deep vein thrombosis) were reported in 74 patients (10.8%) in Group A and 82 (11.9%) in Group B. The most frequently reported clinically relevant TVEs were myocardial infarction, 14 (2.0%) in Group A and 20 (2.9%) in Group B; cerebrovascular accident, 15 (2.2%) in Group A and 15 (2.2%) in Group B; and angina pectoris, 13 (1.9%) in Group A and 13 (1.9%) in Group B.

There were no clinically meaningful changes in clinical laboratory results or vital signs during the study.

CONCLUSION:

The results of this study demonstrated that PROCRIT® treatment to a target hemoglobin of 13.5 g/dL provides no benefit for anemic CKD patients when compared to treatment to a target Hb level of 11.3 g/dL. In this study, patients randomized to a higher target Hb had more composite events, including deaths and hospitalizations for CHF. These results are consistent with prior randomized trials in both pre-dialysis and anemic CKD patients with end-stage renal disease.

Date of the report: 22 September 2006

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