SYNOPSIS

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

Protocol No.: PR04-06-022 (CR002299)

Title of Study: An open-label, randomized study to determine the pharmacokinetic and pharmacodynamic profiles of PROCRIT® (epoetin alfa) in anemic subjects with chronic kidney disease

Principal Investigator: Multicenter study

Publication (Reference): Pharmacokinetic and Pharmacodynamic Profiles of Epoetin Alfa (EPO) in Anemic Subjects with Chronic Kidney Disease. Tracy McGowan, Jessica S. Beaver, Marsha Wolfson. JASN 2007. 18; 758A. SU-PO787

Study Period: 15 February 2006 to 26 November 2006 | **Phase of Development:** I

Objectives: The primary objective of the study was to describe the pharmacokinetic (PK) profiles of 4 different dosing regimens of PROCRIT in subjects with anemia secondary to chronic kidney disease (CKD) not on dialysis.

The four dosing regimens were as follows:

Group A: PROCRIT 50 IU/kg by subcutaneous (SC) injection three times per week (TIW)

Group B: PROCRIT 10,000 IU by SC injection once weekly (QW)

Group C: PROCRIT 20,000 IU by SC injection once every 2 weeks (Q2W)

Group D: PROCRIT 40,000 IU by SC injection once every 4 weeks (Q4W)

The secondary objective was to describe the pharmacodynamic (PD) response to the four PROCRIT study dosing regimens using the following outcomes: absolute and % reticulocyte count, hemoglobin (Hb), hematocrit (Hct), and red blood cell (RBC) count. Safety also was assessed.

Methodology: This was a prospective, open-label, randomized, multicenter, PK/PD study in subjects with anemia secondary to non-dialysis CKD.

The study had 3 phases: screening, open-label treatment, and a study completion/early withdrawal phase. In the screening phase, subjects could be evaluated up to 14 days prior study entry. The treatment phase began when the subject was randomized and continued until last study drug dose. The study completion/early withdrawal phase included the last study-related procedures (Study Day 64 for the Q4W group and Study Day 36 for all other dosing regimens). The PK and PD sampling was performed as per the Time and Events schedule.

Number of Subjects (Planned and Analyzed): A total of approximately 40 CKD subjects were to be enrolled in this study. The sample size chosen for this study was similar to that used in other PK/PD studies of PROCRIT. It was not chosen based on statistical considerations. Subjects were to be enrolled until at least 32 PK-evaluable subjects completed the study, with a minimum of 8 PK-evaluable subjects in each treatment group.

A total of 39 subjects were randomized (10 subjects each in Groups A, C, and D, and 9 subjects in Group B). There were 38 subjects who received at least one dose of PROCRIT and were included in the Safety Population (one subject in Group C did not receive any doses of study medication). The PK-Evaluable Population included 36 subjects and the PD-Evaluable Population included 35 subjects.

Diagnosis and Main Criteria for Inclusion: Adult CKD subjects who were anemic (Hb <11.0 g/dL) at screening and who had not received erythropoietic agents within 6 weeks prior to study entry were eligible to participate. Subjects with CKD (glomerular filtration rate between 15 and 60 mL/min/1.73m^2 and stable creatinine) were selected with the expectation that they would not need dialysis during the course of the study and had sufficient iron stores at study entry.

Main Criteria for Exclusion: Clinically significant systemic disease or laboratory chemistry abnormalities; primary hematologic disease; history of thrombotic vascular event; history of seizure disorder (uncontrolled by medication); uncontrolled hypertension (e.g., systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg); current diagnosis of anemia due to blood loss; untreated chronic folate or Vitamin B_{12} deficiency; any condition that would compromise the ability to respond to erythropoietin therapy; or use of any erythropoietin product or experimental drug or device within 30 days prior to admission.

SYNOPSIS (CONTINUED)

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (PROCRIT®) was supplied as a 1-mL vial containing 10,000 IU epoetin alfa and 2.5 mg human albumin (batch/lot number R13320), a 1-mL vial containing 20,000 IU epoetin alfa and 2.5 mg human albumin (batch/lot numbers R13321 and R13901), or a 1-mL vial containing 40,000 IU epoetin alfa and 2.5 mg human albumin (batch/lot numbers R13322 and R13902). In Group A the dose was 50 IU/kg by SC injection TIW; in Group B the dose was 10,000 IU by SC injection QW; in Group C the dose was 20,000 IU by SC injection Q2W; and in Group D the dose was 40,000 IU by SC injection Q4W.

Duration of Treatment: The duration of treatment was 4 weeks in Groups A, B, and C, and 8 weeks in Group D.

Criteria for Evaluation:

PHARMACOKINETICS:

A PK-evaluable subject was defined as a subject who received the first scheduled administration of study drug, had at least 75% of the PK samples collected up to and including Study Day 29 for all groups, and did not receive any RBC transfusions prior to Study Day 8. The PK evaluations included maximal serum concentration of erythropoietin (C_{max}), time to reach maximal serum concentration (t_{max}), terminal half-life ($t_{½}$), area under the serum concentration-time curve (AUC), and apparent clearance after SC administration (CL/F). The PK evaluations continued through Study Day 29 for Groups A, B, and C and Study Day 57 for Group D.

PHARMACODYNAMICS:

The protocol defined a PD-evaluable subject exactly the same as a PK-evaluable subject; however, one subject was further excluded from PD analysis secondary to unavailable baseline PD values. The PD evaluations included Hb, Hct, total RBC count, and reticulocyte count (absolute and %). The PD evaluations continued through Study Day 36 for Groups A, B, and C and through Study Day 64 for Group D.

SAFETY:

Safety was monitored by physical examinations, vital signs, clinical laboratory tests, and the incidence and severity of any adverse events (AEs). Safety monitoring continued through 30 days after the last visit for all treatment groups.

Statistical Methods:

No formal statistical comparisons were planned for this study. Descriptive summary statistics were used.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

Following SC administration of the initial dose of each regimen, serum erythropoietin concentrations peaked 12 to 24 hours postdose and increased proportionally with increasing dose. Previous single-dose studies of PROCRIT in healthy volunteers reported similar findings: C_{max} was achieved within 24 hours, regardless of dose and the value of C_{max} increased dose-proportionately. After the final dose of the first week in each treatment group of this study (i.e., Study Day 5 for 50 IU/kg TIW (Group A) and Study Day 1 in all other treatment groups), erythropoietin concentrations declined multi-exponentially to baseline values by approximately Study Day 8. Mean $t_{1/2}$ values were similar across the three treatment groups with extended dosing. It was difficult to estimate the $t_{1/2}$ value for 50 IU/kg TIW (Group A) or to compare it to those of the extended dosing regimens; serum erythropoietin concentrations had not reached the terminal elimination phase at the time of the next dose.

Over the 4-week study period, approximately the same cumulative total dose was administered to subjects in each treatment group. However, the pharmacokinetic results showed that systemic exposure increased with extended dosing. Compared to the 50 IU/kg TIW (Group A) dosing regimen, estimated systemic exposure over the 4-week study period was 16%, 50%, and 103% higher for the 10,000 IU QW (Group B), 20,000 IU Q2W (Group C), and 40,000 IU Q4W (Group D) regimens, respectively. This indicates that there was a decrease in systemic clearance, an increase in systemic bioavailability, or both, with increasing dose or less frequent dosing (via extended regimens).The following table summarizes the mean (SD) estimates for the PK parameters for each treatment group:

PK Parameter		50 IU/kg TIW for 4 weeks (n=10)	10,000 IU QW for 4 weeks (n=7)	20,000 IU Q2W for 4 weeks (n=9)	40,000 IU Q4W for 8 weeks (n=10)
C_{max}	(mU/mL)	75.9 (18.1)	193 (104)	368 (166)	1246 (647)
t_{max}[a]	(h)	12.00 (8.95-27.00)	24.00 (12.00-24.00)	24.00 (12.00-72.00)	24.00 (23.98-27.00)
AUC_{last}	(mU.h/mL)	3565 (1157)[d]	10419 (4377)[e]	25275 (14418)[f]	68908 (27238)[g]
$t_{1/2}$	(h)	43.2 (7.65)[b]	28.7 (9.94)	30.6 (22.5)	27.2 (17.6)[b]
λ_z	(1/h)	0.0166 (0.00312)[b]	0.0272 (0.0105)	0.0292 (0.0115)	0.0325 (0.0150)[b]
CL/F	(mL/h)	1386 (425)	1103 (425)	961 (450)[c]	600 (193)[c]

[a] Median (range); [b] n=9; [c] n=7

[d] Represents data up to approximately 72 hours.; [e] Represents data up to approximately 168 hours.

[f] Represents data up to approximately 336 hours.; [g] Represents data up to approximately 672 hours.

SYNOPSIS (CONTINUED)

PHARMACODYNAMICS:

Pharmacodynamic markers of erythropoietin activity were assessed at specified times for each regimen as a tool for comparison of maximal and overall response as well as the time course of response over the treatment period. The following table summarizes the mean (SD) maximum response (R_{max}) and overall response (AUR_{last}) values for absolute reticulocyte count and percent reticulocytes.

PD Marker Parameter	50 IU/kg TIW for 4 weeks (n=9)	10,000 IU QW for 4 weeks (n=7)	20,000 IU Q2W for 4 weeks (n=9)	40,000 IU Q4W for 8 weeks (n=10)
Absolute Reticulocyte				
R_{max} ($x10^6/\mu L$)	0.0691 (0.0192)	0.0856 (0.0405)	0.0656 (0.0285)	0.0899 (0.0466)
AUR_{last} ($x10^6.h/\mu L$)	20.7 (7.74)	28.6 (17.3)	21.9 (14.9)	20.9 (14.3)
Percent Reticulocyte				
R_{max} (%)	1.80 (0.433)	2.04 (1.12)	1.91 (0.867)	2.14 (1.16)
AUR_{last} (%.h)	493 (208)	656 (369)	625 (488)	453 (329)

While differences in the values for each of the reticulocyte markers were observed across the treatment groups, it should be noted that the sample sizes in each treatment group were small and the variability in response was high. Overall response across groups was generally similar.

The following table presents mean (SD) maximum response (R_{max}) and AUR_{last} values for percent Hct, Hb, and total RBC count.

PD Marker Parameter	50 IU/kg TIW for 4 weeks (n=9)	10,000 IU QW for 4 weeks (n=7)	20,000 IU Q2W for 4 weeks (n=9)	40,000 IU Q4W for 8 weeks (n=10)
Percent Hematocrit				
R_{max} (%)	4.22 (1.99)	4.43 (2.23)	4.22 (2.39)	4.70 (2.21)
AUR_{last} (%.h)	1673 (1298)	1765 (1072)	1904 (1382)	2701 (1612)
Hemoglobin				
R_{max} (g/dL)	1.13 (0.316)	1.19 (0.701)	1.10 (0.678)	1.26 (0.638)
AUR_{last} (g.h/dL)	534 (284)	471 (332)	468 (373)	744 (481)
Total Red Blood Cell Count				
R_{max} ($x10^6/\mu L$)	0.344 (0.181)	0.371 (0.250)	0.389 (0.252)	0.500 (0.211)
AUR_{last} ($x10^6.h/\mu L$)	164 (138)	145 (139)	162 (139)	331 (205)

Mean maximal and mean overall response, based on percent Hct, Hb, and total RBC count, in subjects receiving 50 IU/kg TIW (Group A), 10,000 IU QW (Group B) or 20,000 IU Q2W (Group C) were similar. This response was higher in subjects receiving 40,000 IU Q4W (Group D) relative to the mean response in the other groups. As seen with the reticulocyte response, there was substantial variability in percent Hct, Hb, and total RBC count across the regimens.

SYNOPSIS (CONTINUED)

SAFETY:

Of the 38 subjects enrolled in the study, 21 (55%) experienced at least one AE. The incidence of AEs was similar between treatment groups. The most common AEs were peripheral edema in 5 subjects (13%); and gout, back pain, rheumatoid arthritis, headache, and hypertension each in 2 subjects (5%). Investigators did not consider any AE to be related to study drug.

Adverse Events Experienced by More than One Subject

	Group A 50 IU/kg TIW for 4 weeks (n=10) n (%)	**Group B 10,000 IU QW for 4 weeks (n=9) n (%)**	**Group C 20,000 IU Q2W for 4 weeks (n=9) n (%)**	**Group D 40,000 IU Q4W for 8 weeks (n=10) n (%)**	**All (N=38) n (%)**
At least one AE	5 (50)	5 (56)	4 (44)	7 (70)	21 (55)
Peripheral edema	1 (10)	2 (22)	1 (11)	1 (10)	5 (13)
Gout	0	0	0	2 (20)	2 (5)
Back Pain	0	1 (11)	1(11)	0	2 (5)
Rheumatoid arthritis	0	1 (11)	0	1 (10)	2 (5)
Headache	0	0	0	2 (20)	2 (5)
Hypertension	1 (10)	0	0	1 (10)	2 (5)

Three subjects experienced a total of 5 serious adverse events (hyperkalemia, myocardial infarction, gout, cellulitis and edema), none of these were considered treatment related. There were no deaths.

CONCLUSION:

The PK values of erythropoietin in CKD patients were similar to the PK values observed in previously studied populations of healthy subjects or anemic cancer patients. Over the 4-week study period, approximately the same cumulative total dose was administered to subjects in each treatment group. The PK results showed that systemic exposure increased with extended dosing and that there is a decrease in systemic clearance, an increase in systemic bioavailability, or both, with increasing dose or less frequent dosing. However, all extended dosing regimens resulted in comparable PD responses for each of the markers evaluated, indicating that the extended dosing intervals of QW, Q2W and Q4W represent useful alternatives to the TIW dosing regimen without loss of PD effect.

The higher PROCRIT doses used with QW, Q2W, and Q4W dosing regimens in this study had comparable safety profiles to the approved dosing regimen of PROCRIT for CKD patients.

Issue Date of the Clinical Study Report: 18 Dec 2007

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