SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C. NAME OF FINISHED PRODUCT: PROCRIT NAME OF ACTIVE INGREDIENT(S): Epoetin Alfa	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: PR02-33-048

Title of Study: Comparative Pharmacokinetic and Pharmacodynamic Study of Epoetin Alfa [PROCRIT®] in Anemic Critically Ill Patients Randomized to One of Six Dose Regimens for 15 Days

Coordinating Investigator: Not Applicable

Publication (Reference): Not Applicable

Studied Period (years): Clinical Conduct: 18 May 2004 to 27 February 2006 | **Phase of Development:** 2

Objectives: The primary objective of this study was to describe the pharmacokinetic (PK) profile of 6 different dosing regimens of epoetin alfa (PROCRIT) in anemic critically ill subjects, including a regimen that is being used in a large registration trial. The regimens were as follows:

Regimen A: 40,000 IU subcutaneously (s.c.) weekly (q.w.) on Study Days 1, 8, and 15; Regimen B: 40,000 IU intravenously (i.v.) q.w. on Study Days 1, 8, and 15; Regimen C: 15,000 IU s.c. every other day (q.o.d.) on Study Days 1, 3, 5, 7, 9, 11, 13, and 15; Regimen D: 15,000 IU i.v. q.o.d. on Study Days 1, 3, 5, 7, 9, 11, 13, and 15; Regimen E: 40,000 IU s.c. q.o.d. on Study Days 1 and 3, then 15,000 IU s.c. q.o.d. on Study Days 5, 7, 9, 11, 13, and 15; Regimen F: 40,000 IU i.v. q.o.d. on Study Days 1 and 3, then 15,000 IU s.c. q.o.d. on Study Days 5, 7, 9, 11, 13, and 15

The secondary objectives were as follows:

- to describe reticulocyte response (absolute and percentage), hemoglobin (Hb), hematocrit (Hct), and red blood cell (RBC) count response to the 6 PROCRIT dosing regimens.
- to compare the pharmacodynamic (PD) profile of each dosing regimen with the 40,000 IU s.c. q.w. dosing regimen and all dosing regimens.
- to describe the safety profile of each of the 6 dosing regimens.

Methodology: This was a randomized, open-label, parallel-group, multicenter study. Sixty critically ill subjects with anemia were to be accrued to 6 dosing regimens in this study. Computer generated randomization was used to assign subjects to 1 of the 6 dosing regimens. Blood samples were collected at Baseline and at specific times during the study to measure serum erythropoietin (EPO) concentrations, hematology parameters, absolute number and percentage of reticulocytes, serum chemistries, and iron parameters. Subjects participated in the study for a maximum of 28 days. No study drug dosing occurred after Study Day 15, but blood sampling for PD parameters continued through Study Day 28. All adverse events occurring through Study Day 28 were collected. Also, all blood transfusion information was collected from the day of hospital admission through Study Day 28 regardless of subject location within the hospital at the time of transfusion. This included all transfusions received by the subject while under emergency department care and those transfusions given at a previous hospital if the subject was transferred.

Number of Subjects (planned and analyzed): This study was designed for approximately 60 subjects. A total of 60 subjects were dosed at 10 study sites.

SYNOPSIS (CONTINUED)

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Diagnosis and Main Criteria for Inclusion: Subjects must have satisfied the following criteria at study Screening: the subject was critically ill and either admitted to a critical care area with a medical diagnosis (nonsurgical and nontrauma) without evidence of acute blood loss, or admitted for surgery or trauma and developed a medical diagnosis and had no current transfusion needs and no evidence of active bleeding for the prior week; the subject had an expected hospital stay of at least 7 days beyond study entry; the subject was at least 18 years of age; the subject had a serum Hb of 12 g/dL or less; the subject had no blood transfusions within 1 week (7 days) before administration of PROCRIT; the subject was either a male or infertile female (sterile or postmenopausal [defined as the absence of menses for at least 1 year] and must have had a negative pregnancy test at Screening); the subject had no history of deep vein thrombosis or pulmonary embolism; the subject was not moribund; the subject had no acute cardiac or neurological disease; and the subject must have agreed to informed consent after the nature of the study had been fully explained to the subject and/or a legally authorized representative.

Test Product, Dose and Mode of Administration, Batch No.:

Epoetin alfa (PROCRIT) was formulated as a sterile, colorless, preservative-free, phosphate or citrate solution (40,000 IU/mL) or as a colorless solution with preservative (20,000 IU/mL) and was supplied in single- or multiple-use vials. PROCRIT 20,000 IU/mL (Batch numbers R12481;D04LA1182 and R12692/04072) and 40,000 IU/mL (Batch numbers R12480;D03LG1096, R12691/04072 and R13417;14612.1) solutions were used. The study drug was administered as either an s.c. injection or an i.v. infusion based upon dosing group assignment. When administered i.v. PROCRIT was diluted to 10 mL with normal saline in a 10-mL syringe and administered slowly over 10 minutes.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: Maximum duration of treatment of 15 days with a maximum study length of 28 days

Criteria for Evaluation:

Pharmacokinetics: Blood samples were collected at specified times for the determination of serum EPO concentrations. Serum concentrations of EPO were measured by a validated enzyme-linked immunosorbent assay method. The following PK parameters were estimated: observed maximum serum concentration (C_{max}), time to achieve C_{max} (t_{max}), mean trough concentration from samples obtained before dosing (C_{min}), area under the serum EPO concentration versus time curve from time zero to 48 hours after dosing for Groups C, D, E, and F (AUC_{48}) and zero to 168 hours after dosing for Groups A and B (AUC_{168}), terminal elimination half-life ($t_{1/2}$), total clearance of drug after i.v. administration (CL), bioavailability (F), total clearance of drug after s.c. administration, corrected for apparent clearance (CL/F), and elimination rate constant (λz).

Pharmacodynamics: Changes from Baseline through Study Day 28 in reticulocytes (percentage and absolute number), Hb, and total RBCs were planned to be compared among treatment groups. In addition, the C_{max} and AUCs of PD markers were planned to be compared among treatment groups by descriptive statistics.

Pharmacokinetics/pharmacodynamics: Relationships between exposure to EPO (mean AUC of EPO) in the PK-evaluable population and extent of reticulocytes, Hb, and total RBC count of the PD-evaluable population (mean AUCs of the PD parameters) were planned to be explored by graphical methods.

Safety: Evaluations included assessment of the incidence and intensity of treatment-emergent adverse events, clinical laboratory tests, and vital sign measurement results.

Other: In order to evaluate the PD response in relationship to the status of the subject the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) II assessments were used to evaluate the degree of organ dysfunction and to score severity of subject illness.

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Statistical Methods: Descriptive summary statistics including graphical presentations were used to evaluate the PK and PD profiles of EPO.

Populations:

Pharmacokinetic Population: The PK-evaluable population included subjects who received all scheduled study drug before the full PK blood sampling period and had at least three fourths of the scheduled PK blood samples drawn. Subjects who were randomly assigned to a treatment arm but who withdrew from the study before receiving the study drug were excluded from the PK analysis. The baseline serum EPO concentration was the measurement from the blood sample obtained 30 minutes before dosing on Study Day 1.

Pharmacodynamic Population: The PD population included subjects who received all scheduled doses of study drug and had values determined for at least three fourths of the PD hematology assessments, with the last assessment at or beyond Study Day 15.

Safety Population: All subjects who received at least 1 dose of the study drug were included in the safety population for safety analysis.

Evaluations:

Pharmacokinetics: For each subject, individual serum EPO concentration versus time profiles were plotted. Mean serum concentration-time profiles were plotted for each treatment. Mean concentrations of EPO for each dosing group alone and all dosing groups together were plotted as a function of dose. The mean C_{max}, AUC_{48}, AUC_{168}, CL, and CL/F values were plotted as a function of dose. Serum concentrations at each time point and estimated PK parameters were summarized with mean, median, minimum, maximum, SD, and coefficient of variation (CV) for each treatment. Bioavailability values were summarized by dosing group.

Pharmacodynamics: The PD analyses included the pattern of change in reticulocytes (absolute and percentage), Hb, Hct, and RBC indices (mean corpuscular volume, mean corpuscular Hb, and mean corpuscular Hb content), which were evaluated and compared using graphical techniques and descriptive statistics.

Safety: All subjects who received at least 1 dose of the study drug were included in the safety analyses. The number of subjects with at least 1 adverse event and the number of subjects under each system organ class and preferred term were tabulated through Study Day 28. All adverse events were summarized by relationship to the study drug. The number of subjects with adverse events and number of subjects under each system organ class and preferred term were summarized by intensity.

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Summary – Conclusions

Disposition: A total of 60 subjects were enrolled in this study and received study drug. All groups were assigned 9 or 10 subjects with the exception of dosing Group B, which had 13 subjects assigned. Of the 60 subjects enrolled in the study 17 (28.3%) completed the study and 43 (71.7%) discontinued the study. The majority of the discontinuations (25) were designated as "Other" and included subjects who were either discharged from the hospital and did not complete dosing (13), or were discharged from the hospital and completed dosing but discharge data were unavailable (11), or were given a do not resuscitate order and treatment was withdrawn (1). Three subjects were discontinued because of loss to Follow-up.

Demographics: The study population was 60% male (36/60) and 61.7% Caucasian (37/60), ranged in age from 21 to 82 years with a mean age of 52.5 years, and had a mean Body Mass Index of 33.3 kg/m^2 (SD 17.82 kg/m^2, range 15 to 121 kg/m^2). Approximately 90% of the subjects had medical histories that included respiratory, cardiovascular, endocrine/metabolic, blood/lymphatic, and psychological/psychiatric disorders.

Pharmacokinetic Results: Mean (SD) PK parameters and dose regimen values for the s.c. and i.v. dose administration are presented in the following tables:

Parameters		Treatment A 40,000 s.c. weekly n=9	Treatment B 40,000 i.v. weekly n=12
C_{max}	(mU/mL)	434 (290)	19398 (20512)
t_{max}	(h)	22.30 (12.96)	0.60 (0.85)
AUC_{last}	(mU.h/mL)	24682 (11426)	190148 (90108)
AUC_{168}	(mU.h/mL)	24328 (12162)[a]	185095 (92706)[c]
AUC_{∞}	(mU.h/mL)	26815 (12083)[b]	190647 (90123)
$t_{1/2}$	(h)	24.5 (5.46)[b]	9.49 (2.38)
CL/F[d]	(mL/h)	1.86 (1.04)[b]	0.258 (0.119)
λ_z		0.0297 (0.00737)[b]	0.0778 (0.0209)

[a] n=8

[b] n=6

[c] n=11

[d] CL for Treatment B.

Mean C_{max} for the i.v. dose (dosing Group B) was approximately 45-fold higher compared with the C_{max} for the s.c. dose (dosing Group A). There was a high degree of variability (%CV=105%) in peak concentrations for the i.v. dose, dosing Group B, as compared with concentrations for the s.c. dose (%CV=66%), dosing Group A. Systemic exposure measures represented by AUCs were approximately 6- to 8-fold higher for the i.v. dose compared with the s.c. dose group. Apparent clearance (CL/F) after s.c. administration was approximately 8-fold higher than systemic clearance estimated after i.v. administration, owing to the confounding factor of bioavailability. Mean t_{max} for the s.c. dose was slower than the i.v. dose. The mean $t_{1/2}$ was longer by almost 2- to 3-fold for s.c. administration (dosing Group A) compared with i.v administration (dosing Group B), likely due to continuing absorption and elimination after s.c. administration.

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Parameters		Treatment C 15,000 s.c. q.o.d	Treatment D 15,000 i.v. q.o.d	Treatment E 40,000 s.c./ 15,000 s.c	Treatment F 40,000 i.v./ 15,000 s.c
Day 1		n=9	n=9	n=9	n=9
C_{max}	(mU/mL)	183 (67.9)	3774 (1381)	438 (183)	14961 (7073)
t_{max}	(h)	23.67 (12.40)	0.15 (0.05)	19.37 (12.44)	0.32 (0.34)
AUC_{48}	(mU.h/mL)	5564 (2381)[a]	37447 (13606)[c]	12239 (4371)	155856 (88588)[c]
Day 5		n=7	n=9	n=9	n=6
C_{max}	(mU/mL)	248 (153)	3628 (862)	340 (233)	331 (349)
t_{max}	(h)	12.39 (6.13)	0.15 (0.06)	4.61 (4.54)	1.59 (2.48)
AUC_{48}	(mU.h/mL)	7934 (4939)[b]	31509 (10330)[b]	9424 (6175)	6787 (6460)

[a] n=7

[b] n=6

[c] n=8

When the PK profiles for dosing Groups A and C (s.c. dosing) were compared with the PK profiles of dosing Groups B and D (i.v. dosing), the peak EPO concentrations were approximately 20-fold lower for s.c. dosing. When the PK profiles for dosing Group E (s.c. dosing) were compared with the profile from dosing Group F (s.c. and i.v. dosing) the peak EPO concentrations were approximately 30-fold lower. Overall, there was a relatively low degree of variability in peak EPO concentrations for dosing Groups C and D (%CV range = 36% to 37%) and for dosing Groups E and F (%CV range = 41% to 47%), respectively when compared with dosing Groups A and B. Following administration of PROCRIT on Study Day 1, serum concentrations were generally similar across all s.c. treatments (dosing Groups A, C, and E) or all i.v. treatments (dosing Groups B, D, and F), when normalized for dose.

Pharmacodynamic Results: No formal PD analysis was conducted due to the limited number of evaluable PD samples across all dosing groups. However, individual blood concentration-time profiles of percent reticulocytes, Hb, and total RBCs were summarized. Of the 31 subjects who completed dosing, 3 (Subjects 11-106, 07-103, and 11-105) did not demonstrate appreciable increases in absolute reticulocyte count. The remaining subjects demonstrated a 2- to 8-fold maximal increase in absolute reticulocyte count during the course of the study. The PD parameters of Hb, Hct, and RBC showed either fluctuation or some moderate increases of mean values from Baseline over the course of the study. Individual subject variation was wide and the number of subjects who had PD parameter determinations (Hb, Hct, and RBCs) at Study Days 22 and 28 was small (N=19 and 21 for Study Days 22 and 28, respectively). Individual values are presented in the following table.

Subject	Dosing Group	Reticulocytes Absolute (10^9/L) [a]				Hematocrit [a]		Hemoglobin (g/L) [a]	
		Base-line	Maximum Response (Study Day)		End of Treat-ment	Base-line	End of Treat-ment	Base-line	End of Treat-ment
07-106	A	73.7	221.1	(15)	221.1	0.300	0.397	96	125
11-101	A	76	161	(22)	161	0.324	0.336	104	107
11-113	A	23	164	(15)	86	0.352	0.308	117	103
13-106	A	43.2	168.1	(11)	144.5	0.241	0.324	83	102
14-101	A	ND	ND		ND	0.347	0.323	114	99
02-101	B	ND	ND		ND	0.353	0.316	112	99
02-103	B	ND	ND		ND	0.377	0.325	120	101
03-101	B	28	113	(4)	91	0.234	0.246	76	77
07-101	B	ND	139	(4)	85.8	0.320	0.288	104	94
09-103	B	ND	ND		ND	0.248	0.297	82	94
11-106	B	161	161	(1)	111	0.292	0.349	90	103
13-101	B	39.7	181.1	(11)	58.6	0.323	0.407	105	126
14-102	B	ND	181.26	(15)	181.26	0.252	0.278	78	84
16-101	B	30	210	(15)	150	0.345	0.327	111	104
05-103	C	29.1	237.2	(22)	237.2	0.257	0.352	83	112
11-107	C	37	204	(11)	133	0.296	0.222	98	72
13-102	C	34.1	89.1	(15)	89.1	0.324	0.228	107	72
14-108	C	93.79	191.8	(11)	104.22	0.298	0.368	97	117
03-102	D	23	115	(15)	37	0.272	0.330	92	107
07-103	D	116	149	(4)	7.2	0.259	0.312	86	105
09-102	D	ND	ND		ND	0.280	0.278	93	85
11-105	D	122	125	(11)	94	0.337	0.294	96	84
14-110	D	29.84	113.6	(15)	103.53	0.289	0.308	99	103
05-105	E	62.2	168.3	(8)	168	0.371	0.279	106	92
07-104	E	56	267	(22)	267	0.267	0.266	87	85
11-112	E	14	274	(11)	166	0.297	0.366	102	115
13-105	E	ND	191.9	(8)	116.3	0.229	0.375	74	123
14-105	E	91.52	198.24	(15)	166.5	0.280	0.343	86	98
14-111	E	63.42	150.8	(11)	106.88	0.265	0.293	85	84
05-106	F	77.7	217.7	(11)	157	0.299	0.372	99	121
13-104	F	43.2	114.6	(22)	114.6	0.291	0.333	93	110

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Pharmacokinetic/Pharmacodynamic Relationships: As a result of the limited number of evaluable PD samples across all dosing groups, the planned PK/PD relationship analysis was not performed; however, an exploratory analysis was performed that allowed inclusion of additional subjects' data in a descriptive analysis. The exploratory analysis suggested the following:

- when s.c. and i.v. dosing were compared (dosing Group A versus dosing Group B and dosing Group C versus dosing Group D), s.c. dosing appeared to elicit a more robust reticulocytosis. Thus, the EPO C_{max}, which was at least 10-fold higher in i.v. dosing groups, did not appear to correlate with reticulocyte response.
- within dosing groups, as the EPO AUC_{last} increased, the reticulocyte response appeared to increase. Across dosing groups, the EPO AUC_{last} appeared unrelated to dose.
- the time of peak mean absolute reticulocyte counts occurred on Study Day 11 or 15 in most dosing regimens.

Safety Results:

All 60 subjects receiving study drug were included in the safety population. All subjects received concomitant medications. A total of 1610 medications were taken by the 60 subjects, an average of over 25 medications per subject.

Nineteen subjects experienced a total 26 serious adverse events. Of the 19 subjects who experienced serious adverse events, 13 died. No subjects discontinued because of adverse events. Two subjects experienced 3 clinically significant thrombovascular adverse events (deep vein thrombosis and 2 incidents of chest pain [cardiovascular]).

A total of 56 (93.3%) of 60 subjects experienced adverse events. More subjects experienced the adverse events of pyrexia (11/60), hypokalemia (9/60), and hypophosphatemia (9/60) than any other adverse event. Twenty subjects experienced adverse events of severe intensity. The adverse event of respiratory failure was suffered by more subjects (4/60) than any other adverse events of severe intensity.

The adverse events related to laboratory abnormalities experienced by the largest numbers of subjects were hypokalemia, hypophosphatemia, and hypomagnesemia (experienced by 15.0%, 15.0%, and 11.7% of subjects, respectively).

The study admission criteria of anemia and entry into a critical care facility allowed for section of a population of subjects suffering from a heterogeneous mix of both severe and chronic illnesses. The number of adverse events, deaths, serious adverse events, and abnormal laboratory findings are consistent with this critically ill study population. Only 17 subjects completed the study (completed dosing and study assessments through Study Day 28). The low number of subjects completing the study diminished the usefulness of safety comparisons between dosing groups.

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Conclusion: The following conclusions were drawn from the study results:

- apparent PK differences occurred in the profiles for different dosing groups.
    - the groups receiving i.v. dosing achieved a higher extent of exposure of serum concentrations of EPO and achieved this exposure at a faster rate compared with groups receiving s.c. dosing.
    - on comparison of data from this study with other historical study data, we observed similarities in PK profiles of critically ill subjects with those in healthy subjects, but not with anemic cancer subjects with or without concurrent chemotherapy.
- limited PD data were available in this study, precluding the planned characterization of the relationship between drug exposure and pharmacologic effects for the various dosing regimens studied. However, the following trends were observed in exploratory subsets:
    - s.c. administration appeared to elicit a more robust reticulocytosis when compared with i.v. administration of the same dose.
    - as the EPO AUC_{last} increased, reticulocyte response appeared to increase within each dosing group.
    - most dosing regimens showed a peak mean absolute reticulocyte count on Study Day 11 or 15.
- no apparent differences in the incidence, intensity, or categories of adverse events between dosing groups occurred.
- no apparent differences in the incidence, degree, or categories of abnormal laboratory findings between the different dosing groups occurred.

Date of the report: 20 December 2006