SYNOPSIS

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE	(FOR NATIONAL
Ortho Biotech Clinical Affairs, LLC	REFERRING TO PART OF	AUTHORITY USE ONLY)
	THE DOSSIER	
NAME OF FINISHED PRODUCT:	Volume:	
PROCRIT~ (epoetin alfa) NAME OF ACT IVE INGREDIENT(S):	Page:	
Recombinant human erythropoietin		

Protocol No.: CR002296

Title of Study: A randomized double-blind, placebo-controlled study to evaluate the effect of weekly PROCRIT® (epoetin alfa) on anemia and quality of life in children with cancer undergoing myelosuppressive chemotherapy.

Coordinating Investigators: James Feusner, MD; Pamela Hinds, RN, PhD, Marilyn Hockenberry, PhD, PNP; Jeffrey Hord, MD; Bassem Razzouk, MD; Clinton Stewart, PharmD (Pharmacokinetic/Pharmacodynamic Ancillary Study). See Appendix 1.4.

Publication (Reference):

Freeman BB, Iacono LC, Hinds PS, et al. Pharmacokinetics (PK) of intravenously (IV) administered epoetin alfa in pediatric patients receiving myelosuppressive chemotherapy [abstract]. Proc Am Soc Clin Oncol 2004;22:808. (Abs 8552).

Razzouk BI, Hockenberry M, Hinds PS, et al. A double-blind, placebo-controlled study of once-weekly epoetin alfa in children with cancer undergoing myelosuppressive chemotherapy [abstract]. Proc Am Soc Clin Oncol 2004;22:801. (Abs 8527).

Razzouk BI, Hockenberry M, Hinds PS, et al. Influence of hemoglobin response to epoetin alfa on quality-of-life in anemic children with cancer receiving myelosuppressive chemotherapy [abstract]. Blood 2004; 104:609a (Abs 2218).

Study Initiation/Completion Dates: 05 September 2000 - 04 September 2003	**Phase of development:** 3b

Objectives: To evaluate the efficacy and safety of once weekly dosing of PROCRIT on anemia and quality of life (QoL) in children with malignant solid tumors, Hodgkin's disease, acute lymphocytic leukemia (ALL), or non-Hodgkin's lymphoma (NHL). These patients were either scheduled to receive their first myelosuppressive chemotherapy within 7 days of Baseline or had received up to the second myelosuppressive chemotherapy within 60 days prior to study enrollment.

Methodology: This 16-week study was originally designed as 2 separate randomized, double-blind, placebo-controlled, multicenter studies. Study 1 planned for the enrollment of 220 anemic children with newly diagnosed malignant solid tumor or Hodgkin's disease, while Study 2 planned for the enrollment of 220 anemic children with ALL, or NHL. The studies were later combined into 1 protocol due to slow patient accrual. After the 2 original protocols were combined, randomization was stratified by cancer type, with 1 stratum (protocol stratum 034) for children diagnosed with a malignant solid tumor or Hodgkin's disease, and the second stratum (protocol stratum 044) for children diagnosed with ALL or NHL.

Patients were seen and evaluated based on the patient's scheduled chemotherapy regimen. For patients who were receiving chemotherapy every 3 weeks, scheduled study visits occurred every 3 weeks. This group was labeled as the "3-week group." For patients receiving chemotherapy weekly, every 2 weeks, or every 4 weeks, scheduled study visits occurred every 4 weeks. This group was labeled as the "4-week group." Scheduled study visits took place prior to the start of myelosuppressive chemotherapy administration. All doses of study drug were calculated based on a concentration of 20,000 Units/mL in each vial. The initial dose of study drug was 600 Units/kg for a maximum dose of 40,000 Units administered intravenously once per week. A hemoglobin (Hb) level was drawn just before the start of the chemotherapy dose at Study Week 4 for the 3-week group or Study Week 5 for the 4-week group. If Hb had not increased by at least 1g/dL from the baseline value at Study Week 4 for the 3-week group or Study Week 5 for the 4-week group, then the dose of study drug was increased to 900 Units/kg for a maximum dose of 60,000 Units administered intravenously each week.

Data and Safety Monitoring Board (DSMB): An independent DSMB held quarterly safety reviews in person or by teleconference. In addition, the DSMB met approximately 3 months after completion of the 70th patient in protocol stratum 034 to review interim data for Hb effect.

SYNOPSIS (CONTINUED)

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Ortho Biotech Clinical Affairs, LLC NAME OF FINISHED PRODUCT: PROCRIT~ (epoetin alfa) NAME OF ACT IVE INGREDIENT(S): Recombinant human erythropoietin	Volume: Page:	

Number of Subjects (planned and analyzed): Two hundred twenty pediatric patients with anemia were planned. Two hundred twenty-four patients were enrolled; 222 patients were included in the modified intent-to-treat (MITT) and safety populations.

Diagnosis and Main Criteria for Inclusion: Male or female pediatric (5-18 years of age) patients who were anemic according to age- and gender-based criteria, newly diagnosed with cancer and scheduled to receive their first myelosuppressive chemotherapy within 7 days of Baseline or had received up to the second myelosuppressive chemotherapy within 60 days prior to enrollment. All patients must have met additional inclusion and exclusion criteria.

Test Product, Dose and Mode of Administration, Batch No.: PROCRIT (epoetin alfa) 20,000 Units/mL was formulated as a sterile, buffered solution containing 2.5 mg/mL human serum albumin administered by intravenous injection (i.e., intravenous push) through an existing central venous access device or peripheral intravenous catheter.

Batch numbers for protocol stratum 034: D00LA0267 (package lots R1003 1, R10741), D00LJ0521 (package lots R10877, R11302, R11746), and D02LL0992 (package lot R12038).

Batch numbers for protocol stratum 044: D00LA0267 (package lots R10033, R10743), D00LJ0521 (package lots R10879, R11300, R11748), and D02LL0992 (package lot R12042).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was formulated identically to PROCRIT, except the placebo vials did not contain the active ingredient (epoetin alfa).

Batch numbers for protocol stratum 034: D00LA0265 (package lots R10032, R10742), D00LJ0522 (package lot R10878), D00LM0565 (package lots R11303, R11747), and D02LH0953 (package lot R12039).

Batch numbers for protocol stratum 044: D00LA0265 (package lots R10034, R10744), D00LJ0522 (package lot R10880), D00LM0565 (package lots R11301, R11749), and D02LH0953 (package lot R12043).

Duration of Treatment: A patient was seen and evaluated based on his or her scheduled chemotherapy regimen. For patients who received chemotherapy every 3 weeks, scheduled study visits occurred every 3 weeks and for those who received chemotherapy weekly, every 2 weeks, or every 4 weeks, scheduled study visits occurred every 4 weeks. Scheduled study visits took place prior to the start of chemotherapy administration. Enrolled patients were to start the assigned study drug regimen within 1 week of randomization and were to continue for 16 weeks. Chemotherapy treatments were administered concurrently with study drug treatment for at least 12 weeks as part of the inclusion criteria.

Criteria for Evaluation:

Efficacy: The primary endpoint was the last value total score of the patient-reported PedsQL™ Pediatric Quality of Life (QoL) Inventory (PedsQL Inventory). The primary efficacy analysis was the comparison of PROCRIT versus placebo on the difference between the last value minus the baseline value. The time course of PedsQL evaluations over the course of the study were also explored. The secondary endpoints included parent-reported assessments on the PedsQL Inventory, patient-and parent-reported assessments on the PedsQL™ Cancer Module, Hb levels, and transfusion requirements. Analysis of the secondary endpoints was similar to that of the primary endpoint.

Safety: Safety was assessed by comparing the incidence and severity of adverse events (AEs) in the PROCRIT group versus the placebo group. Clinical laboratory tests (hematology, iron profile, and serum chemistry), physical examinations, and vital sign measurements were also assessed.

Pharmacokinetic/Pharmacodynamic Relationships: All pharmacokinetic/pharmacodynamic analyses and discussion are presented in Appendix 2.4.

SYNOPSIS (CONTINUED)

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NAME OF ACTIVE INGREDIENT(S): Recombinant human erythropoietin	Page:	

Statistical Methods: The MITT approach was used in the statistical analyses. The MITT population includes all patients who entered the study and were randomly assigned to either the PROCRIT or placebo group, received at least 1 dose of study drug, and had at least 1 postrandomization QOL evaluation. The safety population included all patients entered into the study who received at least 1 dose of study drug.

Continuous variables were summarized using descriptive statistics (sample size [n], mean, standard deviation, median, minimum and maximum). Categorical variables were summarized by frequency and proportion.

For the primary endpoint, final values of patient-reported PedsQL Inventory between the PROCRIT and placebo groups were compared using an analysis of covariance (ANCOVA), with baseline patient-reported PedsQL Inventory as a covariate, and study treatment, study site and protocol stratum (034 or 044) as fixed effects. The ANCOVA models were also used to compare the PROCRIT group with the placebo group on the parent-reported PedsQL Pediatric QoL Inventory and the patient and parent-reported assessments on the PedsQL Cancer Module. Post-hoc analyses were conducted to adjust for packed red blood cell (pRBC) transfusion effect by 1) setting QoL to missing if the patient received a pRBC transfusion within 28 days prior to the final value, and 2) in ANCOVA analyses using pRBC transfusion status within 28 days prior to the final QoL as a covariate. Repeated measure analysis using the generalized estimating equations (GEE) approach compared the PROCRIT group with the placebo group on quality of life over time. The correlations analyses were conducted to evaluate the association between the patient- and parent-reported PedsQL Inventory and between the patient- and parent-reported PedsQL Cancer Module. Hemoglobin change from Baseline was summarized for each study week. Hemoglobin change from Baseline to Week 16 and from Baseline to final measurement were compared between the PROCRIT and placebo groups using ANCOVA. The GEE approach was used to further compare the PROCRIT group with the placebo group on Hb over time. The time to 1 g/dL or 2 g/dL Hb increase from Baseline was estimated using the Kaplan-Meier method and compared between the 2 groups using the log-rank test. The relationship between QoL and Hb was explored by summarizing QoL scores for each category of Hb change from Baseline.

The proportions of patients who received at least 1 pRBC or whole blood transfusion were compared between the PROCRIT and placebo groups using Fisher exact test. The volumes or units transfused were compared using an independent sample t test. The frequencies of pRBC/whole blood transfusions administered during the study between the 2 groups were compared using the Mantel-Haenszel chi-square. Time to first pRBC/whole blood transfusion was estimated using the Kaplan-Meier method and compared between the 2 groups using the log-rank test. Subgroup analyses by protocol stratum or by cancer type also were conducted for the primary and secondary variables. Time to first pRBC/whole blood transfusion was estimated using the Kaplan-Meier method and compared between the 2 treatment groups using the log-rank test.

The main analyses for the primary and secondary QoL outcomes used the Last Value Carried Forward method. When computing QoL scores, according to the scaling and scoring guide of the PedsQL Inventory and PedsQL Cancer Module, if more than 50% of any QoL scale data were missing, the total score for that scale was set to missing. No imputation estimates were used in the repeated measures analyses. If Hb data were missing for any scheduled study visit, data from unscheduled study visits were used if that visit occurred within 1 week of the scheduled study visit; otherwise, missing data was not imputed. To eliminate the pRBC transfusion effect on Hb, Hb within 28 days after a pRBC transfusion was set to missing to adjust for the impact of pRBC transfusion on Hb response. All tabulations were performed by treatment group unless otherwise indicated.

SYNOPSIS (CONTINUED)

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PROCRIT~ (epoetin alfa) NAME OF ACT IVE INGREDIENT(S):	Page:	
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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Twenty-seven of 32 sites enrolled 224 patients; 113 were randomly assigned to PROCRIT and 111 to placebo. Two hundred twenty-two patients received at least 1 dose of study drug and had at least 1 postrandomization QOL evaluation, thus were included in the MITT population (111 patients each in the PROCRIT and placebo treatment groups). The safety population included 112 patients in the PROCRIT and 110 in the placebo treatment groups. Patient 33/34140 was randomly assigned to the placebo group but received 1 dose of commercially available PROCRIT during the study. The patient's data were included in the placebo group for the efficacy analyses but were included in the PROCRIT group for the safety analyses. One hundred eighty-four (82.1%) patients completed the study; 40 (17.9%) withdrew from the study early (19 [16.8%] PROCRIT patients; 21 [18.9%] placebo patients). The mean age of patients was 11.6 years. However, on average, placebo patients were 1.6 years younger than the PROCRIT patients (P=0.0017). More than half (54.5%) of patients were male, and 68.5% of patients were Caucasian. Concomitant medications taken by patients spanned multiple therapeutic categories and were consistent with treatment of cancer. Protocol violations did not affect the interpretation of data.

More PROCRIT-treated patients (n=7) had Stage III-B and IV-B Hodgkin's disease compared with placebo-treated patients (n=4). Of the patients with solid tumors, fewer PROCRIT-treated patients (n=1 1) had Ewing's sarcoma compared with placebo-treated patients (n=23). The PROCRIT group had a greater number of patients aged 8 to 18 years with ALL (n=33) than did the placebo group (n=17). Conversely, there were fewer PROCRIT-treated patients aged 5 to 7 years with ALL (n=7) versus placebo-treated patients (n=18). More patients with NHL were in the PROCRIT group (n=14) than in the placebo group (n=8). For both treatment groups, the majority of patients had Stage III NHL (PROCRIT, n=10; placebo, n=6).

Primary Endpoint:

Patient-reported PedsQL Inventory - Overall there was no statistically significant difference between study treatment groups with regard to patient-reported PedsQL Inventory scores. When the data were analyzed by age, patients 5 to 7 years of age who received PROCRIT treatment experienced a significant (P=0. 043 1) improvement in PedsQL Inventory adjusted mean score at Last Value (adjusted mean score=87.98) compared with patients 5 to 7 years of age in the placebo group (adjusted mean score=78.09). This difference in the total score may be attributed to a significant improvement (P=0.0074) in the physical functioning (walking, running, chores, etc) of patients in that age category. This difference in the total score was consistent after adjustment for pRBC transfusion.

Secondary Endpoints:

Parent reported PedsQL Inventory - When parent-reported PedsQL Inventory scores were evaluated for all patients and by patient age categories, there were no statistically significant differences with regard to study drug treatment. Similar results were seen after adjustment for pRBC transfusion or when pRBC transfusions were treated as a covariate.

Patient-reported and Parent-reported PedsQL Cancer Module - Overall, there were no statistically significant differences between PROCRIT and placebo in mean patient-reported or in parent-reported scores for any of the Cancer Module subscales. When pRBC transfusion status was used as a covariate, the model revealed statistically significantly improved patient-reported perceived physical appearance scores for PROCRIT patients aged 13 to 18 years (P=0.0367) and parent-reported perceived physical appearance scores for PROCRIT patients aged 5 to 7 years (P=0.0221).

SYNOPSIS (CONTINUED

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No statistically significant differences between PROCRIT and placebo in mean patient-reported scores for any of the subscales or age categories were seen after excluding values that were obtained within 28 days after a pRBC transfusion. However, there was a statistically significant improvement in parent-reported pain and hurt scores for placebo patients aged 13 to 18 years (*P*=0.0058). There was a statistically significant improvement in PROCRIT patient-reported cognitive problems scores from Baseline at Week 9/10 and at Completion/Early Withdrawal (*P*=0.0 178). For placebo there was a significant improvement in parent-reported cognitive problems scores (*P*=0.0200) from Baseline at Week 9/10, but not at Study Completion/Early Withdrawal.

Correlation between Patient-reported and Parent-reported Quality of Life - There was a correlation between the patient-reported and parent-reported PedsQL Inventory and Cancer Module scores. For the PedsQL Inventory, the correlation coefficient was 0.695 for the total score, 0.770 for the physical subscale score, and 0.588 for the psychosocial subscale score. The correlations between the patient-reported and parent-reported PedsQL Cancer Module scores ranged from 0.339 (treatment anxiety subscale score) and 0.586 (nausea subscale score). All correlations were statistically significant (*P*<0.0001).

Hemoglobin - Mean Hb increases from Baseline to Last Value for all cancer types combined was statistically significant in favor of PROCRIT (*P*=0.0308). Repeated measures analysis revealed that the overall test for differences in the Hb change over time was statistically significant between treatment groups for the combined protocol (034/044) favoring PROCRIT, without adjusting for pRBC transfusion (*P*=0.0017). Similar results were obtained after adjusting for pRBC transfusions.

Kaplan-Meier estimates of the cumulative probability of having a 1 g/dL or 2 g/dL increase in Hb, excluding Hb within 28 days after a pRBC transfusion (all cancer types combined) showed a clear separation in the probability curves favoring PROCRIT. The cumulative probability of having a 2 g/dL Hb increase was statistically significantly higher for PROCRIT versus placebo (*P*=0.0026).

pRBC/Whole blood transfusions – No patients received whole blood during the study. Overall, fewer PROCRIT patients (64.9%) compared with placebo patients (77.5%) received at least 1 pRBC transfusion, although this was not statistically significant. However, significantly fewer PROCRIT than placebo patients received at least 1 pRBC transfusion during Weeks 9-12 (24% vs. 45%, respectively; P=0.0021) and Weeks 13-16 (20% vs. 34%, respectively; P=0.0363).

SAFETY RESULTS: The safety population included patients who received at least 1 dose of study drug (112 PROCRIT patients; 110 placebo patients). Patient 33/34 140 was randomly assigned to treatment with placebo, but received 1 dose of commercially available PROCRIT in error. This patient is included in the PROCRIT safety population for analyses. Patients in both treatment groups were exposed to a similar number of days of treatment and similar numbers of patients in each treatment group reported at least 1 treatment-emergent adverse event AE. Gastrointestinal disorders, such as abdominal pain, mucositis, diarrhea, and vomiting were reported by the greatest number of patients regardless of treatment group. Serious adverse events (SAEs) were reported by 77 (68.8%) PROCRIT patients and 82 (74.5%) placebo patients. Only 8 patients (4 in each treatment group) reported SAEs that were considered related to study drug administration. Patients in general, regardless of treatment group, recovered without sequelae and required no change or interruption of study drug. Thrombotic vascular events (e.g., thrombosis, pulmonary thrombosis, coronary thrombosis) and other clinically significant SAEs occurred infrequently and occurred among similar numbers of patients in both treatment groups. Four patients (2 PROCRIT, 2 placebo) died during the study. Two patients (1 PROCRIT, 1 placebo) discontinued from the study due to a treatment-emergent AE.

SYNOPSIS (CONTINUED)

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CONCLUSION: Overall, administration of PROCRIT in pediatric patients with cancer did not have a statistically significant effect on patient-reported or parent-reported PedsQL Inventory or Cancer Module scores compared with placebo. However, results of the PedsQL Inventory total score at last value showed a statistically significant difference favoring PROCRIT for patients aged 5 to 7 years. The mean hemoglobin change from baseline to last value was significantly greater for PROCRIT patients. While there was no statistical difference between PROCRIT and placebo patients receiving at least 1 pRBC transfusion overall, significantly fewer PROCRIT patients were transfused during Weeks 9 to 12 and Weeks 13 to 16. PROCRIT was safe and well tolerated when administered once weekly as intravenous doses of 600 Units/kg (for a maximum of 40,000 Units) to 900 Units/kg (for a maximum of 60,000 Units) to pediatric patients with cancer.

Date of the report: 13 December 2004

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