NAME OF COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: PROCRIT® (epoetin alfa) NAME OF ACTIVE INGREDIENT(S): Recombinant human erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART ___ OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title of the Study: A Double-Blind, Placebo-Controlled Study to Determine Whether PROCRIT® Epoetin Alfa Can Reduce Perioperative Transfusion Requirements in Subjects Undergoing Major Orthopedic Surgery (Protocol M92-011)

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Publication (Reference): None

Studied Period (Years): 18 April 1993 to 30 August 1994	**Clinical Phase:** III

Objectives: To 1) determine whether epoetin alfa can reduce perioperative allogeneic transfusion requirements in subjects undergoing major orthopedic surgery and to 2) evaluate the safety of epoetin alfa.

Methodology: Multicenter, double-blind, placebo-controlled, parallel-group study, at 26 U.S. centers, that enrolled 316 subjects, who were scheduled for major orthopedic hip or knee surgery and who were expected to require ≥2 units of blood. Subjects were stratified into one of three groups based on their baseline hemoglobin (≤10, >10 to ≤13, and >13 g/dL), then randomly assigned to receive either epoetin alfa or placebo. Study drug was blinded for dose and identity. Subjects received oral iron throughout the trial. Every effort was made not to transfuse subjects with hemoglobin values >9 g/dL, except where clinical symptoms warranted. All subjects received low-dose Coumadin® as prophylaxis against DVTs, and underwent ultrasonography as screening for DVTs.

Number of Subjects (Total and for Each Treatment): 316 total. 112, 101, and 103 subjects were randomly assigned to receive 300 IU/kg epoetin alfa, 100 IU/kg epoetin alfa, and placebo, respectively. Included, in these three treatment groups respectively,: 1, 1, and 0 in the ≤10 g/dL baseline hemoglobin stratum; 35, 30, and 31 in the >10 to ≤13 g/dL stratum; and 76, 70, and 72 in the >13 g/dL stratum.

Diagnosis and Criteria for Inclusion: Subjects (male or female) enrolled in this study were to be at least 18 years old, scheduled for major orthopedic hip or knee surgery, expected to require transfusion of ≥2 units of blood, and unwilling or unable to participate in an autologous predonation program before surgery. They must have read and signed the informed consent form. Female subjects were to be postmenopausal for ≥1 year before study entry, surgically sterile, or using adequate birth control and have had a negative pregnancy test just before study entry. Subjects were to have had a hemoglobin level of ≤15 g/dL, a serum iron:TIBC ratio of ≥15%, and a ferritin level of ≥50 ng/mL. They were not to have clinically significant abnormal values for hematology, serum chemistry, urinalysis, folate, B_{12}, or stool occult blood tests.

Test Product, Dose and Mode of Administration, Batch No.: 300 or 100 IU/kg epoetin alfa administered daily; subcutaneous injection; lot numbers 5305A, R5424A, R5535A, and R5627A.

Duration of Treatment: Daily for 10 consecutive days prior to the day of surgery, on the day of surgery (after surgery), and for four consecutive days immediately following the day of surgery.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo administered daily; subcutaneous injection; lot numbers 5306A, R5426, R5535, and R5669.

Criteria for Evaluation: Efficacy evaluations were based on a comparison of the perioperative allogeneic blood transfusion requirements in each treatment group, overall and within each baseline hemoglobin stratum, and a comparison of changes in hemoglobin, hematocrit and reticulocyte count over time. Safety evaluations included assessments of adverse events, clinical laboratory tests, vital sign measurements, and physical examinations.

Statistical Methods: The primary population for all efficacy evaluations was a modified intent-to-treat population (all subjects who were randomly assigned to a treatment group and who underwent surgery). The initial analysis of the primary efficacy variable was carried out using a logistic regression model for the risk of transfusion in the overall population; further analyses were focused within the prespecified baseline hemoglobin strata, >10 to ≤13 g/dL and >13 g/dL; there were too few subjects for analysis within the ≤10 g/dL stratum. A "step-down" procedure that controlled for the overall family-wise error rate was

Statistical Methods (continued): employed to account for multiple comparisons; the 300 IU/kg epoetin alfa- and placebo-treated groups were compared and tested at the α=0.05 level, and only if this comparison was significant, the 100 IU/kg epoetin alfa- and placebo-treated groups were compared. The mean number of units transfused per subject and the hemoglobin, hematocrit, and reticulocyte levels were the secondary efficacy endpoints. Safety summaries were of adverse events, thrombotic/vascular events, changes in ultrasonography results, and changes in clinical laboratory tests and vital signs.

SUMMARY - CONCLUSIONS:

Demographics: Of the 316 subjects who were randomly assigned to a treatment group (intent-to-treat population), 291 subjects underwent orthopedic surgery of the hip or knee and were thus included in the modified intent-to-treat population that was the basis of the primary efficacy analysis. Demographic and baseline characteristics, types of surgery performed, and prestudy concomitant medications were comparable between the treatment groups and the baseline hemoglobin strata. At least 88% of subjects in each treatment group completed the study.

Efficacy Results: Overall, 11% of subjects who received 300 IU/kg epoetin alfa, 11% of subjects who received 100 IU/kg epoetin alfa, and 23% who received placebo received allogeneic blood. Logistic regression analysis using hemoglobin as a continuous variable indicated that the effect of treatment was not consistent for all baseline hemoglobin values. The focus of further analyses of the primary efficacy variable was within the prespecified >10 to ≤13 g/dL and >13 g/dL baseline hemoglobin subgroups; the results are presented in the following table.

Percentage of Subjects Who Received Allogeneic Transfusions

	No. (%) of Subjects			p value	
Baseline Hemoglobin Stratum	300 IU/kg Epoetin Alfa	100 IU/kg Epoetin Alfa	Placebo	300 vs. Placebo	100 vs. Placebo
>10 to ≤13 g/dL Stratum	(N=31)	(N=26)	(N=29)		
	5 (16%)	6 (23%)	13 (45%)	0.024	0.155
>13 g/dL Stratum	(N=68)	(N=68)	(N=67)		
	6 (9%)	4 (6%)	9 (13%)	0.426	Not tested[a]

[a] Not tested in this multiple comparison framework because the 300 IU/kg vs. placebo result was not significant.

In the >10 to ≤13 g/dL stratum, a significantly (p=0.024) lower proportion of subjects were transfused among 300 IU/kg epoetin alfa-treated (16%) than among placebo-treated subjects (45%); the response was dose-related. A smaller proportion of epoetin alfa-treated than placebo-treated subjects in the >13 g/dL stratum were transfused (not statistically significant).

The mean number of units transfused per epoetin alfa-treated subject was smaller than the mean transfused per placebo-treated subject (overall p=0.0278). The mean hemoglobin levels, hematocrit levels, and reticulocyte counts were higher in the epoetin alfa-treated groups than in the placebo-treated group throughout the trial, indicative of increased erythropoiesis in response to treatment with epoetin alfa. During the prestudy to presurgery period, in both strata, mean increases in hemoglobin, hematocrit, and reticulocyte counts in both epoetin alfa-treated groups were observed while generally no changes were observed in the placebo-treated groups (between-group p=0.0001).

Safety Results: The use of epoetin alfa in orthopedic surgery subjects was safe and well tolerated. The most common adverse events were pyrexia, nausea, and constipation. Overall, the incidence of adverse events was comparable across treatment groups and across baseline hemoglobin strata. A higher incidence of DVTs was detected in 300 IU/kg epoetin alfa subjects (9%) who had a baseline hemoglobin of >13 g/dL compared with placebo-treated subjects (0%) in this stratum; however, the rate was within the published rates for DVT incidence. In the population with a baseline hemoglobin of >10 to ≤13 g/dL, DVT rates were similar between epoetin alfa-treated (11%) and placebo-treated subjects (16%).

There were no notable differences across treatment groups or baseline hemoglobin strata with regard to 1) the rates of subject discontinuation from the study because of adverse events or 2) the rates of serious or unexpected adverse events. Discontinuation rates due to adverse events were 6%, 3%, and 4% in the 300 IU/kg epoetin alfa-treated group, 100 IU/kg epoetin alfa-treated group, and placebo-treated group, respectively. Serious or unexpected events were observed in 6% of subjects in each epoetin alfa-treated group and 8% of subjects in the placebo-treated group. One death was reported; a 300 IU/kg epoetin alfa-treated subject suffered an MI eight days after his last dose of study medication (i.e., study completion) and died two days later; the relationship of this event to study drug was classified by the investigator as unlikely. There were no clinically significant findings when comparing treatment groups with regard to clinical laboratory results or vital signs results.

Conclusions: The results of this study indicate that epoetin alfa, at a dose of 300 IU/kg for 10 days prior to, on the day of surgery, and for four days after surgery, results in a significantly lower incidence of exposure to allogeneic blood transfusion when compared with placebo treatment in a population of subjects who have a baseline hemoglobin of >10 to ≤13 g/dL and who are undergoing orthopedic surgery of the hip or knee. The dosing regimen of epoetin alfa was well tolerated in this subject population with a safety profile similar to that seen with placebo treatment. A higher incidence of DVTs was detected in 300 IU/kg epoetin alfa subjects who had a baseline hemoglobin of >13 g/dL compared with placebo-treated subjects in this stratum; however, the rate was within the published rates for DVT incidence. In the population with a baseline hemoglobin of >10 to ≤13 g/dL, DVT rates were similar between epoetin alfa-treated and placebo-treated subjects.

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