# SYNOPSIS

| NAME OF SPONSOR/COMPANY: | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
|---|---|---|
| Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and Ortho Biotech Products, LP<br>NAME OF FINISHED PRODUCT:<br>PROCRIT® (Epoetin alfa)<br>NAME OF ACTIVE INGREDIENT(S):<br>Recombinant Human Erythropoietin | Volume:<br>Page: | |

**Protocol No.:** PR98-15-014

**Title of Study:** Efficacy of rHuEPO (Epoetin Alfa) in the Critically Ill Patient: A Randomized, Double-Blind, Placebo-Controlled Trial

**Principal Investigator(s):** Andrew Gettinger, M.D., and Howard L. Corwin, M.D. [redacted].
65 investigators participated, 62 investigators enrolled subjects.

**Study Center(s):** 65 centers in U.S.A.

**Publication (Reference):** None

**Studied Period (years):** 19 December 1998 to 18 July 2001

**Phase of development:** 3

**Objectives:** The purpose of this study was to determine whether the administration of rHuEPO (epoetin alfa) to critically ill patients would result in a decrease in the number of subjects receiving any RBC transfusion and a decrease in the cumulative number of RBC units transfused.

**Methodology:** This was a multicenter, randomized, double-blind, placebo-controlled study. Subjects were evaluated for entry into the study on ICU Day 2, and were randomly assigned to receive placebo or epoetin alfa (40,000 IU/dose). All hospitalized subjects were to receive a dose of study drug on Study Days 1 (ICU Day 3 or 4), 7, and 14. Subjects in the ICU on Study Day 21 received a fourth dose for a maximum of 4 doses. The need for blood transfusion was determined by the subject's attending physician. No transfusion was to be given for a hematocrit >27% unless a specific indication was also present. All subjects were to receive iron supplementation.

**Number of Subjects (planned and analyzed):** 1,300 planned; 1,302 enrolled and analyzed for safety and efficacy.

**Diagnosis and Main Criteria for Inclusion:** Subjects were to be 18 years or older with a hematocrit <38%. If a subject met the entry requirements on ICU Day 3 (or on ICU Day 4, if in the opinion of the investigator the subject could benefit from epoetin alfa therapy), the subject was to be enrolled in the study. Female subjects were to have been postmenopausal for at least 1 year, surgically sterile, or if of childbearing potential were to have had a negative pregnancy test immediately before study entry. The study was to be explained to subject or family and a consent form was to be signed.

**Test Product, Dose and Mode of Administration:** Epoetin alfa (PROCRIT® 20,000 U/mL) was formulated as a sterile, colorless, preserved, buffered solution containing 2.5 mg/mL human serum albumin. Each vial contained approximately 1.1 mL of study drug of 20,000 U/1 mL. Study drug (40,000 IU/dose epoetin alfa or placebo) was administered by s.c. injection beginning on ICU Day 3 (Study Day 1). All hospitalized subjects were to receive a dose of study drug on Study Days 1, 7, and 14. An additional dose was administered on Study Day 21 to subjects who were in the ICU during the same hospital admission. No subjects were to receive more than a maximum of 4 doses of study drug. Study drug was held if the hematocrit drawn within 24 hours prior to dosing was >38%. Bulk Lot Nos.: D00LA0266, D99LG0149, and R7298 for the 20,000 U/mL (1-mL vials).

**Duration of Treatment:** 28 days. Subjects were to be followed for the occurrence of adverse events through Day 42. Safety data were collected prospectively on all subjects for Days 1 through 28, however, for Days 29 through 42 safety data were collected prospectively only on the 549 subjects enrolled following implementation of the August 2000 protocol amendment, with retrospective collection on the 753 subjects enrolled prior to this amendment.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Placebo was formulated as a sterile, colorless, preserved, buffered solution containing 2.5 mg/mL human serum albumin without epoetin alfa. Bulk Lot Nos. for placebo: D00LM0565, D00LJ0522, D00LA0265, D99LG0147, and R7299.

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| NAME OF ACTIVE INGREDIENT(S): | Page: | |
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**Criteria for Evaluation:**

Efficacy: The primary efficacy end point, transfusion independence was to be assessed by comparing the proportion of subjects in the 2 treatment groups receiving any RBC transfusion from Study Day 1 through Day 28. Secondary efficacy end points included the cumulative (number of RBC units) transfusions received through Study Day 28, cumulative mortality through Study Day 28, time to first RBC transfusion or death, change in hemoglobin from baseline to last dosing-related value, proportion of subjects receiving non-RBC transfusions, mechanical ventilator usage, ICU length of stay (LOS), and hospital LOS. In addition, the potential impact of transfusion practice on the primary efficacy end point (percent of subjects transfused) was explored in the context of the results reported by in the Transfusion Requirement in Critical Care (TRICC) trial (Hebert et al. 1998).

Safety: Safety evaluations included assessments of the incidence and severity of adverse events including deaths, thrombotic vascular events, and clinical laboratory tests (hematology, iron parameters, and serum chemistry).

**Statistical Methods:** Fisher's Exact Test was to be used for the primary analysis of the primary efficacy end point (proportion of subjects transfused) along with the 95% confidence interval (CI) for the estimated treatment effect. Logistic regression analysis was to be used to generate an adjusted treatment effect and to explore possible prognostic effects of relevant baseline variables. In addition, time pattern of transfusions (i.e., time from baseline to first RBC transfusion) was to be explored using Kaplan-Meier estimates and log rank test.

Wilcoxon-Mann-Whitney test was to be applied to compare the cumulative number of RBC units transfused between the 2 treatment groups. To account for the variable amount of time that subjects were on study, hence at risk of receiving transfusions, transfusion rate (in terms of total number of RBC units) per day alive was to be calculated. Treatment difference was to be tested using normal distribution theory along with the 95% CI.

Analyses of cumulative mortality were to include Kaplan-Meier estimates and log rank test. In addition, Cox regression was to be used to generate an adjusted treatment effect and to explore possible prognostic effects of relevant baseline variables. Similar analyses were to be performed for time to first RBC transfusion or death.

Change in hemoglobin from baseline to last dosing-related hemoglobin value was to be compared between the 2 treatment groups using the Student's t-test along with 95% CI for the difference. To assess treatment effect with respect to the pattern of hemoglobin over time, a mixed effect linear model for the longitudinal data of hemoglobin over time was to be utilized. Proportion of subjects receiving non-RBC transfusions was to be compared between the 2 treatment groups using Fisher's Exact Test.

Mechanical ventilator use was assessed for the total number of mechanical ventilation-free days from Day 1 through Day 28 and the following time-to-event variables: time from Day 1 to discontinuation of initial mechanical ventilation for subjects who were on mechanical ventilator at Day 1; time from Day 1 to new onset of mechanical ventilation for subjects who were not on mechanical ventilator at Day 1; and time from discontinuation of initial ventilation to reventilation. ICU LOS assessments included total number of ICU-free days from Day 1 to Day 28 and the following time-to-event variables: time from Day 1 to initial discharge from ICU; and time from initial ICU discharge to ICU readmission. Hospital LOS was analyzed as a time-to-event variable. Total number of ventilation-free days and total number of ICU-free days were analyzed using Wilcoxon tests. All time-to-event variables were analyzed using Kaplan-Meier estimates and log rank test.

In order to compare the primary efficacy result from the current study to the TRICC trial, descriptive analysis on percent of subjects transfused was provided in a subgroup of subjects in the current study who would have met the eligibility criteria used in the TRICC trial, i.e. baseline hemoglobin <9.0 g/dL. In addition, to assess the potential impact of the use of a more restrictive transfusion policy (hemoglobin 7.0 to 9.0 g/dL) on the primary efficacy end point, descriptive analysis was conducted on percent of subjects transfused, where a subject was considered transfused only if the transfusion was performed when the subject's hemoglobin had fallen below a specified threshold. To compare the results of the present study with the results reported in the TRICC trial, the focus of this analysis was on the subgroup of subjects with baseline hemoglobin <9.0 g/dL.

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**SUMMARY – CONCLUSIONS**

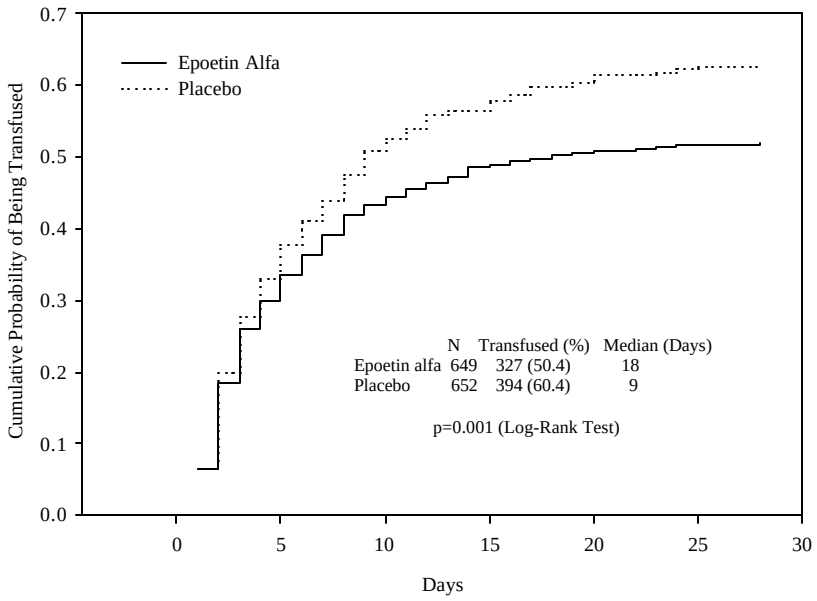
One thousand three hundred two subjects were enrolled. By randomization in 1:1 ratio, 652 subjects were assigned to receive placebo and 650 subjects were assigned to receive epoetin alfa. These 1,302 subjects were included in the intent-to-treat population.

Demographic characteristics were generally comparable between the epoetin alfa and placebo treatment groups with respect to age, sex, race, and weight. For all subjects, the mean age was 51.3 years, and more men than women were enrolled (61.9% vs. 38.1%). Overall, the time in the ICU prior to the first dose of study drug, the APACHE II score, the admitting diagnoses, and the medical history were generally comparable between the epoetin alfa and placebo treatment groups. The mean APACHE II score was 19.6±7.79. Trauma (48.4%) and postoperative care (45.2%) were the 2 most common admitting diagnoses. Hematology and serum chemistry parameters at baseline were comparable between the 2 treatment groups. The mean baseline hemoglobin concentration was 9.97±1.18 g/dL (range, 3.5-14.6 g/dL).

EFFICACY RESULTS:

Proportion of Subjects Transfused from Study Day 1 through Day 28: The percentage of subjects receiving RBC transfusions was significantly lower among subjects assigned to the epoetin alfa group compared with subjects in the placebo group (50.5% vs. 60.4%, p=0.0004 by Fisher's Exact Test; relative risk of transfusion 0.84, 95% CI [0.76, 0.92]). Logistic regression analysis yielded an adjusted odds ratio of 0.65 with a 95% CI of (0.51, 0.83). Time (in days) to first RBC transfusion (Figure) was significantly delayed for epoetin alfa group compared with the placebo (median 18 vs. 9 days, p=0.001 by log rank test).

**Figure:** Time to First Transfusion
(Study PR98-15-014: Subjects in the Intent-to-Treat Population)



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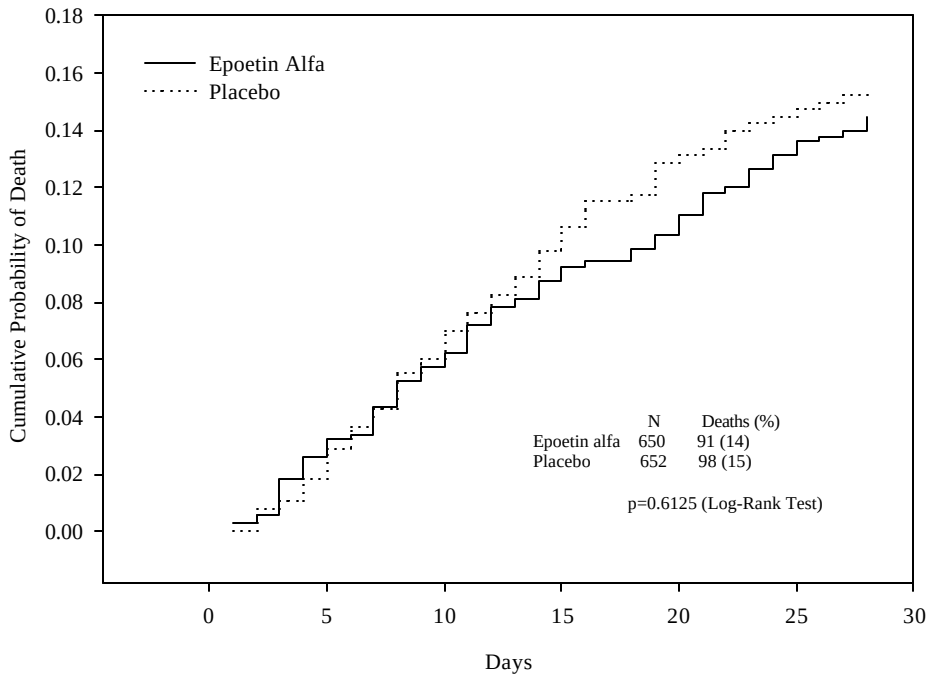
Cumulative Blood Transfusions Received Through Day 28: Total number of RBC units transfused were 1,590 units for the epoetin alfa group and 1,963 units for the placebo group. The cumulative number of RBC units received per subject was significantly lower in the epoetin alfa group compared with the placebo (median 1.0 vs. 2.0 units, p=0.0008 by Wilcoxon-Mann-Whitney test). Transfusion rate per day alive was also significantly lower in the epoetin alfa group compared with the placebo group (0.098 vs. 0.121, p=0.04). Ratio of RBC transfusion rates per day alive was 0.809 with 95% CI of (0.646, 0.973), indicating a 19.1% (i.e., 1 – [0.809]) relative reduction in transfusion burden for the epoetin alfa group when compared with the placebo group.

Cumulative Mortality Through Day 28: Mortality through Day 28 was 14% in the epoetin alfa group as compared with 15% in the placebo group (Figure). Treatment difference was not statistically significant (p=0.6125 by log rank test). A Cox regression model adjusting for covariate main effects also showed no significant difference in mortality between the 2 treatment groups (adjusted hazard ratio 0.87, 95% CI [0.64, 1.18], p=0.3689).

**Figure:** Time to Death
(Study PR98-15-014: Subjects in the Intent-to-Treat Population)




Time to First Transfusion or Death: The percentage of subjects who received their first RBC transfusion or who died was 55% in the epoetin alfa group as compared with 65% in the placebo group. Time (in days) to first RBC transfusion or death (Figure) was significantly delayed for epoetin alfa group as compared with the placebo (median times 13 vs. 8, p=0.0014 by log rank test). A Cox regression model showed that after adjusting for covariate main effects, the adjusted hazard ratio was 0.79, (95% CI [0.68, 0.92], and p=0.0026).

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Change in Hemoglobin from Baseline to Last Dosing-Related Value: The mean change in hemoglobin from baseline to last value was significantly greater among subjects in the epoetin alfa group as compared with those in the placebo group (mean increase±SD 1.32±2.02 g/dL vs. 0.94±1.92 g/dL, p=0.001 by the 2-sample t-test). An analysis using a mixed effect linear model for the longitudinal data demonstrated that the rate of increase in hemoglobin over time was significantly greater among subjects in the epoetin alfa group as compared with subjects in the placebo group (difference 0.014 g/dL/day, p=0.0071).

Proportion of Subjects Receiving non-RBC Transfusions: There was no statistically significant difference in percentage of subjects receiving non-RBC transfusions between the epoetin alfa and the placebo groups (15.8% vs. 15.2%, p=0.759 by Fisher's Exact Test).

Mechanical Ventilator Usage, ICU LOS, and Hospital LOS: No statistically significant differences were found between the 2 treatment groups in the assessments of mechanical ventilation use. However, subjects in the epoetin group had 2 more days free of mechanical ventilation use (22 days vs. 20 days) and fewer subjects in the epoetin alfa group required new onset of mechanical ventilation (20.83% vs. 24.44%), and reventilation (16.58% vs. 20.50%) when compared with the placebo group.

No statistically significant differences were found between the 2 treatment groups in the assessments of length of ICU stay. However, subjects in the epoetin group had 1 more day alive and not in the ICU than subjects in the placebo group (18 days vs. 17 days). The percent of subjects who required readmission into the ICU was also lower for the epoetin alfa group when compared with the placebo group (9.83% vs. 13.32%).

The median time to hospital discharge was 21.0 days in the placebo group and 19.0 days in epoetin alfa group. The total number of deaths through hospital discharge was 113 (17.4%) for the placebo group and 103 (15.9%) for the epoetin alfa group.

Potential Impact of Transfusion Policy on the Primary Efficacy End Point A comparison of the results from the current study to those obtained in the TRICC trial, showed that the percent of subjects transfused in the placebo group in the current study was similar to that observed in the restrictive transfusion group reported in the TRICC trial (66.9% vs. 67.0%). This suggests that, for this subgroup, the transfusion practice as utilized in the current study was more similar to the restrictive strategy used in the TRICC trial rather than to that used in the liberal group in which subjects received transfusion when hemoglobin level was 10 to 12 g/dL (in whom 100% were transfused).

Also, the results suggest that the impact of epoetin alfa on the percent of subjects transfused would have been similar across the spectrum of potential transfusion practices using different hemoglobin thresholds. In fact, these analyses may underestimate the benefits of epoetin alfa, to the extent that epoetin alfa therapy may have prevented a fall in hemoglobin to below 7.0 g/dL in subjects who were transfused at higher hemoglobin levels.

SAFETY RESULTS:

Safety data were collected prospectively on all subjects for Days 1 through 28, however, for Days 29 through 42 safety data were collected prospectively only on the 549 subjects enrolled following implementation of the August 2000 protocol amendment, with retrospective collection on the 753 subjects enrolled prior to this amendment.

As expected among ICU patients, the majority of subjects were reported to have at least 1 adverse event during the 42-day safety follow up (544 [83%] of the 652 subjects receiving placebo, and 538 [83%] of the 650 subjects receiving epoetin alfa). The incidence of all treatment-emergent adverse events was comparable between the placebo and epoetin alfa groups. There was no category of adverse event, whether grouped by body system or by preferred term, for which the incidence in subjects receiving epoetin alfa exceeded that in subjects receiving placebo by more than 10 (2%) subjects. Overall, the incidence for all thrombotic vascular events was less in subjects receiving epoetin alfa than in subjects receiving placebo.

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SAFETY RESULTS (continued):

The most frequently affected body systems were the respiratory system (51%), resistance mechanism disorders (33%), and gastrointestinal system (29%). The body systems with the greatest differences between treatment groups were body as whole (27% of those receiving placebo vs. 22% of subjects receiving epoetin alfa), gastrointestinal system (31% of those receiving placebo vs. 28% of subjects receiving epoetin alfa), urinary system (26% of those receiving placebo vs. 23% of subjects receiving epoetin alfa), and the vascular system (13% of those receiving placebo vs. 10% of subjects receiving epoetin alfa), for all these events the incidence was greater in the placebo group. The most frequently reported adverse events by preferred term were pneumonia (22%), sepsis (19%), and urinary tract infection (17%). The preferred terms with the greatest differences between groups were fever (12% of those receiving placebo vs. 8% of subjects receiving epoetin alfa), and pleural effusion (9% of those receiving placebo vs. 6% of subjects receiving epoetin alfa), in each of these events the incidence was greater in the placebo group.

The majority of the adverse events were reported during Days 1 through 28, with only 209 (16.1%) of the subjects reported to have an adverse event during Days 29 through 42. The percent of subjects reported to have an adverse event during Days 29 through 42 was only slightly higher among those who had these events ascertained prospectively than those whose events were ascertained retrospectively (18% vs. 15%). The data do not suggest that conclusions regarding the frequency of adverse events were substantially impacted by the retrospective collection of Day 29 through 42 data in 753 of the 1302 subjects.

There were a total of 212 (16.3%) subjects who died during the 42-day safety follow-up period (100 [15.4%] among subjects in the epoetin alfa group vs. 112 [17.2%] among subjects in the placebo group). Most (189) of the deaths occurred during the initial 28 days of follow up (i.e. the period when all subjects had prospective ascertainment of vital status). During Days 29 through 42, the percent of subjects who died was greater for those with prospective follow up than for those with retrospective follow up (3.1% vs. 0.8%), suggesting that mortality ascertainment was more complete when performed prospectively. However, during Days 29 through 42, the percent of subjects who died was slightly lower among subjects in the epoetin alfa group than those in the placebo group for both subjects whose data were collected prospectively (2.5% vs. 3.6%) and for those whose data were collected retrospectively (0.5% vs. 1.1%). In addition, there were 14 subjects (8 in the epoetin group, 6 in the placebo group) who died after Day 42 but before hospital discharge. Also, there were 4 subjects (3 in the epoetin group, 1 in the placebo group) who discontinued from the study who subsequently died before hospital discharge. Subject [redacted] in the epoetin alfa group died in the rehabilitation unit after the 42-day safety follow-up period.

Comparison of changes in laboratory studies from baseline through the end of the study did not reveal any clinically important differences between the treatment groups or raise any safety concerns regarding the use of epoetin alfa in this population.

CONCLUSION: Administration of epoetin alfa resulted in an increase in the number of subjects who were transfusion free and an almost 20% reduction in the total number of units of RBCs transfused. Despite a significantly lower percent of subjects transfused and significantly fewer RBC units received than the placebo group, subjects receiving epoetin alfa showed a greater increase in hemoglobin from baseline to last value. Epoetin alfa treatment was well tolerated and there were no differences between the epoetin alfa and placebo groups either in mortality, or in frequency or incidence of any adverse event.

Date of the report: 28 FEBRUARY 2002