

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C. <u>NAME OF FINISHED PRODUCT:</u> PROCRT® (Epoetin Alfa) <u>NAME OF ACTIVE INGREDIENT(S):</u> Recombinant human erythropoietin (r-Hu-EPO)	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
Protocol No.: EPO-ICU-002 Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Epoetin Alfa in Critically Ill Subjects		
Coordinating Investigator: Howard Corwin, M.D. – Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA		
Publication (Reference): None		
Study Initiation/Completion Dates: 24 December 2003/19 June 2006	Phase of development: 3	
<p>Objectives: The primary objective was to determine whether the administration of epoetin alfa to critically ill subjects reduced the proportion of subjects requiring red blood cell (RBC) transfusion as compared with placebo. Secondary objectives included a comparison of epoetin alfa- and placebo-treated subjects with regard to the following end points: cumulative number of units of RBC transfusions received from Day 1 through Day 42, change in hemoglobin concentration from Day 1 through Day 29, mortality through Day 29, and cumulative mortality through Day 140.</p> <p>Safety objectives included assessment of the tolerability and safety of a 40,000 IU once-a-week dosing regimen, with particular emphasis on longer-term clinical and laboratory safety follow-up after Day 29. In addition, the incidence of erythropoietin antibodies at baseline and at Day 42 was determined for subjects exposed to either epoetin alfa or placebo.</p>		
<p>Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Critically ill subjects admitted to hospital intensive care units (ICUs) who met all study inclusion and exclusion criteria were randomly assigned in a 1:1 ratio to receive weekly (Days 1, 8, and 15) subcutaneous (s.c.) treatment with either epoetin alfa 40,000 IU or a matching volume of placebo. Randomization was stratified by study center and mutually exclusive ICU admission type (trauma, surgical non-trauma, or medical non-trauma). Subjects with a predose hemoglobin concentration less than 12 g/dL received a weekly dose of study drug for a maximum of 3 doses or until they were discharged from the hospital where dosing was initiated, whichever came first. On Days 8 and 15, study drug was to be withheld if a subject's hemoglobin concentration, measured within 24 hours before dosing and at least 1 hour after any RBC transfusion the subject may have received, was 12 g/dL or greater. Weekly assessments of safety and efficacy were performed on Days 8, 15, 22, and 29. Follow-up safety assessments were performed 6 weeks and 5 months after the first dose of study drug (on Days 42 and 140).</p>		
<p>Number of Subjects (planned and analyzed): 1,460 subjects were planned and enrolled. Efficacy analyses were performed on the intent-to-treat population (N=1,460), which was defined as all randomized subjects. The safety population (N=1,448) was defined as all randomized subjects who received at least 1 dose of study drug.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Subjects were at least 18 years old, critically ill, in need of intensive treatment, admitted to an ICU, and had a hemoglobin concentration of less than 12 g/dL. Subjects were eligible for the first dose of study drug within 48 to 96 hours of their initial ICU admission. If a subject was being re admitted to the ICU, he or she was considered for enrollment if the duration of previous ICU admission was less than 72 hours, the time out of the ICU was 24 hours or more, and the subject could receive the first dose of study drug within 96 hours after the start of his or her ICU re admission. Female subjects were to be postmenopausal for at least 1 year; surgically sterile or otherwise incapable of pregnancy; or, for those of childbearing potential, had to be practicing an acceptable method of contraception for at least 1 month before study entry.</p>		

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<p>Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa was provided as a sterile, colorless, preservative-free phosphate solution. Each single-use vial contained approximately 1 mL of epoetin alfa at a concentration of 40,000 IU/mL. Epoetin alfa was administered subcutaneously, once weekly, at 40,000 IU (international units). The batch numbers for epoetin alfa were R13693, R13457, R12652, and R11977.</p>		
<p>Reference Therapy, Dose and Mode of Administration, Batch No.: The batch numbers for matching placebo were R13694, R13458, R12653, and R11978. The dose and mode of administration matched those of the test product (see above).</p>		
<p>Duration of Treatment: Two-week treatment period consisting of once weekly doses of epoetin alfa 40,000 IU or placebo (Days 1, 8, and 15), followed by posttreatment safety assessments at 6 weeks and 5 months after the first dose of study drug (Days 42 and 140, respectively).</p>		
<p>Criteria for Evaluation:</p> <p><u>Pharmacokinetics:</u> Blood samples were collected from subjects at preselected study centers to measure trough erythropoietin concentration before each administration of study drug and at each follow-up evaluation. Study centers were selected for this evaluation so as to allow the collection of trough erythropoietin concentration data from approximately 300 subjects distributed approximately equally across the 3 mutually exclusive ICU admission types (trauma, surgical non-trauma, and medical non-trauma).</p> <p><u>Efficacy:</u> The primary efficacy criterion was the proportion of subjects requiring RBC transfusions from Day 1 through Day 29. Secondary criteria included the cumulative number of units of RBC transfusions received from Day 1 through Day 42, change in hemoglobin concentration from Day 1 through Day 29, the proportion of subjects who died through Day 29, and cumulative mortality through Day 140.</p> <p><u>Safety:</u> Evaluations were to include assessments of the incidence and severity of adverse events, clinical laboratory tests, vital sign measurements, and physical examination findings. Serum erythropoietin antibodies were also measured. In addition, information regarding surgical/invasive procedures and pneumatic compression use was collected.</p>		
<p>Statistical Methods: Descriptive statistics (mean and standard deviation) of the trough serum erythropoietin concentrations were tabulated; formal analysis of the pharmacokinetic data was not performed.</p> <p>The proportion of subjects requiring RBC transfusions was tabulated as the percentage of subjects in each treatment group who received at least 1 transfusion over the 29-day efficacy follow-up period. Estimates of treatment effects (and their 95% confidence intervals) included the difference in percentages of subjects transfused (epoetin alfa group – placebo group) and the ratio (relative risk) of subjects transfused (epoetin alfa group/placebo group). Treatment groups were compared inferentially using a Cochran-Mantel-Haenszel test, stratified by type of ICU admission (trauma, surgical non-trauma, and medical non-trauma).</p> <p>For the analysis of the cumulative units of RBC transfusions received from Day 1 through Day 42, the Wilcoxon-Mann-Whitney test was used to inferentially compare the 2 treatment groups.</p> <p>An analysis of covariance (ANCOVA) model was used to inferentially compare the mean changes in hemoglobin concentration from Day 1 through Day 29 for the 2 treatment groups. Effects for the baseline hemoglobin concentration, type of ICU admission, and treatment group were included in the model.</p> <p>To assess mortality through Day 29, the proportion of subjects who died between Days 1 and 29, inclusive, in each treatment group was compared inferentially using a Cochran-Mantel-Haenszel test, stratified by type of ICU admission.</p>		

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<p>Statistical Methods: (continued)</p> <p>Kaplan-Meier plots of the cumulative mortality through Day 140 and inferential comparison using the log rank test were provided.</p> <p>Safety data, including adverse events, clinical laboratory test results, vital sign measurements, and results of serum erythropoietin antibody testing, were summarized. The proportions of subjects who underwent surgical/invasive procedures and those who required pneumatic compression were also summarized.</p>		
<p>SUMMARY – CONCLUSIONS: Demographic and baseline characteristics were comparable between the 2 treatment groups. Trauma was the most frequently reported admission type (54.3% for trauma, 22.6% for surgical non-trauma and 23.1% for medical non-trauma). Overall, the time in ICU prior to first dose of study drug, the APACHE II score, the admitting diagnoses, and medical history were comparable between the epoetin alfa and placebo groups. Hematology and serum chemistry at baseline were comparable between the 2 treatment groups, with a mean hemoglobin concentration of 9.6 g/dL for both treatment groups.</p> <p><u>PHARMACOKINETICS:</u> For all subjects, in both the epoetin alfa and placebo groups, the highest mean trough concentrations were attained on Day 1 and generally declined from Day 1 until the final sample collection with no discernable differences between the 2 treatment groups after Day 22. Generally, mean trough levels were slightly higher on Days 8 and 15 (dosing days) and marginally higher on Day 22 for the epoetin alfa-treated subjects compared to placebo-treated subjects. Only on Day 8 the concentrations were consistently higher for all subjects receiving epoetin alfa compared with subjects receiving placebo for all 3 admission type categories.</p> <p><u>EFFICACY RESULTS:</u></p> <p><u>Primary Efficacy Analyses:</u></p> <p>RBC transfusions were received by 48.3% of subjects in the placebo group and 46.0% of subjects in the epoetin alfa group from Day 1 through Day 29 (p=0.341; relative risk for RBC transfusion for the epoetin alfa group, 0.95; 95% confidence interval [CI] [0.85, 1.06]). When subjects who withdrew or died were considered as transfused rather than not transfused, transfusion rates were 57.1% and 52.7% for the placebo and epoetin alfa groups, respectively (p=0.080; relative risk for RBC transfusion for the epoetin alfa group, 0.92; 95% CI [0.84, 1.01]).</p> <p><u>Secondary Efficacy Analyses:</u></p> <p>The cumulative RBC units transfused per subject through Day 42 were similar for both groups (mean: 2.1 units, p=0.695) with total units transfused 1,530 and 1,525 in the placebo and epoetin alfa groups, respectively. A significantly higher (p<0.001) mean hemoglobin increase was seen in the epoetin alfa group from baseline through Day 29 (mean hemoglobin increase 1.20 g/dL in the placebo and 1.58 g/dL in the epoetin alfa group).</p> <p>Mortality through Day 29 was 11.4% in the placebo group compared with 8.5% in the epoetin alfa group (p=0.053). The difference was consistent across all admitting diagnoses (6.6% and 3.5% in the trauma group, 8.3% and 6.2% in the surgical non-trauma group, and 25.6% and 22.5% in the medical non-trauma group). The lower mortality rate in the epoetin alfa group was primarily attributable to the lower mortality rate in the epoetin alfa-treated subjects in the trauma subgroup. Mortality through Day 140 was 16.8% in the placebo group compared with 14.2% in the epoetin alfa group (p=0.113).</p>		

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<p><u>EFFICACY RESULTS:</u> (continued)</p> <p><u>Protocol Specified Exploratory Analyses:</u></p> <p><u>Transfusion Analyses:</u> There were no clinically relevant differences in the proportions of subjects requiring RBC transfusions between the placebo and epoetin alfa groups in any of the ICU admission categories, and no clinically relevant dose-related differences in the proportion of subjects requiring RBC transfusions were noted between the 2 treatment groups.</p> <p>The percentages of subjects transfused by Day 29 for the placebo and epoetin alfa groups were 48.3% and 46.0%, respectively (p=0.539) and confirmed the results of the primary efficacy analysis. The RBC units transfused per subject through Day 29 were similar for both groups (mean: 2.0 versus 1.9 units in the placebo and epoetin alfa groups, respectively; p=0.608).</p> <p><u>Change in Hemoglobin:</u> Mean hemoglobin increased by 1.66 g/dL in the placebo group and by 1.95 g/dL in the epoetin alfa group from baseline through Day 42 (p<0.001) and increased by 2.41 g/dL in the placebo group and 2.63 g/dL in the epoetin alfa group from baseline through Day 140 (p=0.014). Mean reticulocyte levels rose in both treatment groups through Day 15 with a more substantial and continued elevation noted in subjects in the epoetin alfa group through Day 22. Levels were similar between the 2 treatment groups from Day 29 through Day 140.</p> <p><u>ICU and Hospital Length of Stay and Readmissions:</u> No difference in ICU length of stay was noted for subjects from Day 1 through Day 42 or from Day 1 through Day 140 (median for both treatment groups: 8 days; p=0.362 and p=0.425, respectively). Rates of ICU readmission for the placebo and epoetin alfa groups were similar (6.9% and 7.4% respectively; p=0.710). No difference in hospital length of stay was noted in the 2 treatment groups from Day 1 through Day 42 or from Day 1 through Day 140 (median for both treatment groups and both study periods: 15 days; p=0.433 and p=0.370, respectively).</p> <p><u>Mechanical Ventilation Analyses:</u> The proportion of subjects no longer requiring mechanical ventilation was statistically significantly lower in the epoetin alfa group than the placebo group (p=0.010 for Days 1 through 42 and p=0.016 for Days 1 through 140), although this difference was not clinically meaningful (98.4% versus 96.6% for both study periods). The median duration of mechanical ventilation was similar for subjects in the placebo and epoetin alfa groups (7 days and 8 days, respectively) from Days 1 through 42 and from Days 1 through 140. Rates of re-ventilation were similar between the placebo and epoetin alfa groups from Day 1 through Day 42 (19.6% and 20.0%; p=0.851) and from Day 1 through Day 140 (21.8% and 22.3%; p=0.796). Rates of ventilations for subjects who were not on mechanical ventilation on Day 1 and were later placed on ventilation, were similar for the subjects in the epoetin alfa and placebo groups from Day 1 through Day 42 (12.3% and 15.0%, respectively; p=0.381) and from Day 1 through Day 140 (13.2% and 15.5%, respectively; p=0.469).</p> <p><u>Additional Analyses:</u></p> <p>The percentages of subjects transfused from Days 1 to 29, excluding subjects with use of commercially available erythropoietins on or before Day 29, were 46.8% and 44.1% for the placebo and epoetin alfa groups, respectively (p=0.279). Trauma subjects who received epoetin alfa had a significantly lower mortality rate through Day 29 than those who received placebo (3.5% versus 6.6%; p=0.042). The mortality rate through Day 140 was also lower for trauma subjects in the epoetin alfa group compared with the placebo group (6.0% versus 9.2%; p=0.085).</p>		

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<p><u>SAFETY RESULTS:</u></p> <p>The safety population included all subjects who received at least 1 dose of the study drug and for whom safety information was available. Of the 1,460 subjects enrolled in the study, 1,448 were eligible for safety evaluation.</p> <p>A total of 230 (15.9%) subjects (125 [17.4%] subjects in the placebo group and 105 [14.4%] subjects in the epoetin alfa group) died between Days 1 and 140. The most frequently reported causes of death included respiratory failure, cardiac/circulatory failure, sepsis, and “other”. None of the deaths were judged by the investigator to be related to treatment with the study drug.</p> <p>The overall incidence rates of treatment-emergent adverse events were similar for the placebo (680 subjects, 94.4%) and epoetin alfa (690 subjects, 94.8%) groups.</p> <p>Overall, 43.5% of subjects in the placebo group and 44.0% of subjects in the epoetin alfa group had at least 1 treatment-emergent serious adverse event during the study. A total of 14 subjects (5 placebo and 9 epoetin alfa) reported treatment-emergent serious adverse events that were considered related to the study drug by the investigator. The events occurred across all age groups. The events, with 1 exception, affected the circulatory/pulmonary systems, specifically the development of thromboses, pulmonary embolisms, thrombophlebitis, and cerebrovascular disorder. No action was taken regarding the study drug in any of the events and the majority of events were considered resolved by the end of the study.</p> <p>Of the 203 subjects with reported clinically relevant thrombotic vascular events, more subjects in the epoetin alfa group (11.5% and 16.5% in the placebo and epoetin alfa groups, respectively) reported at least 1 clinically relevant treatment-emergent thrombotic vascular event. Although the proportions of subjects with clinically relevant thrombotic vascular events who died was similar in both treatment groups at Days 29 and 40, the absolute numbers of deaths in subjects with clinically relevant thrombotic vascular events was greater for subjects in the epoetin alfa group at both time points.</p> <p>Additionally, clinically relevant thrombotic vascular events were less frequent in subjects receiving heparin at baseline, overall and for all admission types.</p> <p>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.</p>		

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<p><u>CONCLUSIONS:</u></p> <ul style="list-style-type: none"> • No transfusion benefit was observed with epoetin alfa treatment. However, the mean change in hemoglobin concentration from baseline to Days 29, 42, and 140 was greater in the epoetin alfa group than the placebo group. • The epoetin alfa group had lower mortality rates than the placebo group through Days 29, 42, and 140. The improvement in mortality was primarily a result of a mortality benefit in the trauma subgroup. The reported causes of death were as expected in an intensive care population. • There were no clinically meaningful differences between the treatment groups in the duration of mechanical ventilation, the proportions of subjects with re-ventilations or new ventilations, or in the length of ICU or hospital stay. • Overall, rates of treatment-emergent adverse events and reports of degree of intensity and relationship to study drug were generally similar between the 2 treatment groups. • Rates of treatment-emergent serious adverse events were generally similar between the 2 treatment groups. • More subjects in the epoetin alfa group than the placebo group had clinically relevant thrombotic vascular events during the study. However, clinically relevant thrombotic vascular events were less frequent among subjects receiving heparin at baseline, overall and across all admission type categories. • No new, unexpected, substantial, or clinically significant laboratory results were reported. <p>Date of the report: 28 March 2007</p>		

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