SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Ortho-McNeil Pharmaceutical Inc.</td><td rowspan="3">Individual Trial Table Referring to Part of the Dossier:
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Page:</td><td rowspan="3">(For National Authority Use only):</td></tr>
<tr><td>Name of Finished Product:
Epoetin Alfa (r-HuEPO)</td></tr>
<tr><td>Name of Active Ingredient:
erythropoietin</td></tr>
<tr><td colspan="3">Protocol No: CR005902
Title of Study: A double-blind, placebo-controlled study to determine the safety of r-HuEPO (epoetin alfa) and whether r-HuEPO can reduce post-operative transfusion requirements in subjects undergoing major orthopedic surgery</td></tr>
<tr><td colspan="3">Investigators: 20 principal investigators; all investigators enrolled subjects</td></tr>
<tr><td colspan="3">Study Centres: 20 centers</td></tr>
<tr><td colspan="3">Publications (Reference): None</td></tr>
<tr><td colspan="2">Studied Period: December 1989 – October 1991</td><td>Phase of development: 3</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to determine the safety and efficacy of epoetin alfa in reducing the need for blood transfusions after major orthopedic surgery.
The primary efficacy objective was the proportion of patients in each treatment group, overall, and within each baseline hematocrit group requiring blood transfusion following major orthopedic surgery, and comparison of changes in hematocrit and reticulocyte counts from baseline to the end of the study.
The secondary objective of this study was the safety profile, assessed by clinical laboratory tests, vital sign measurements, incidence and severity of adverse events from baseline to the end of the study.</td></tr>
<tr><td colspan="3">Methodology: This was a randomized, double-blind, placebo-control, parallel group, multicenter study conducted in the United States. Subjects were assigned to one of four treatment groups (epoetin alfa 300 or 100 IU/kg/day or the equivalent volumes of placebo) in a 2:1 ratio according to a computer-generated randomization schedule stratified by study center and by a subject's requirement for being scheduled for major orthopedic surgery.
Efficacy evaluations included assessments 4 days following surgery (post-therapy) and 2-3 weeks and 3-4 weeks following surgery (post-study) of the proportion of patients in each treatment group, overall, and within each baseline hematocrit group requiring blood transfusion following major orthopedic surgery, and comparison of changes in hematocrit and reticulocyte counts from baseline to the end of the study
Safety evaluations included incidence and severity of treatment-emergent adverse events, and changes from admission to posttherapy in clinical laboratory test results and in physical examination.</td></tr>
<tr><td colspan="3">Number of Subjects (planned and analyzed): Planned enrollment: 180 evaluable subjects. Enrolled: 200 subjects evaluable for safety, 185 evaluable for efficacy (54 subjects received epoetin alfa 300 IU/kg, 64 subjects received epoetin alfa 100 IU/kg, and 67 subjects received placebo.</td></tr>
<tr><td colspan="3">Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years of age or older undergoing major orthopaedic surgery; expected requirement of ≥2 units of red blood cells; unwilling or unable to participate in an autologous transfusion program prior to surgery; no clinically significant abnormal hematology, chemistry, or urinalysis laboratory tests; hematocrit ≤45%</td></tr>
<tr><td colspan="3">Test Product, Dose and Mode of Administration, Batch Number:
Epoetin alfa 100 IU/kg or 300 IU/kg SC once daily for 14 days</td></tr>
<tr><td colspan="3">Duration of Treatment: 7 to 10 days</td></tr>
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Reference Therapy, Dose and Mode of Administration, Batch Number:
Placebo matching volume of 100 IU/kg or 300 IU/kg SC once daily for 14 days

Criteria for Evaluation:

Efficacy:

Assessments 4 days following surgery (post-therapy) and 2-3 weeks and 3-4 weeks following surgery (post-study) of reduction in the number of subjects requiring transfusions of homologous blood

Reduction in the mean number of units of homologous blood transfused per subject

Greater (positive) change from prestudy to presurgery for hemoglobin, hematocrit, and reticulocyte count

Safety:

Incidence and severity of treatment-emergent adverse events, and changes from admission to posttherapy in clinical laboratory test results and in physical examination.

Statistical Methods:

The primary efficacy variables were the reduction in the number of subjects requiring transfusions of homologous blood, reduction in the mean number of units of homologous blood transfused per subject, and greater (positive) change from prestudy to presurgery for hemoglobin, hematocrit, and reticulocyte count.

The safety variables included incidence, severity, and type of adverse events during the study and changes in physical findings and laboratory measurements from pre-therapy to post-therapy.

There were no statistically significant ($p = 0.05$) differences among the treatment groups with regard to sex, ethnic origin, type of surgical procedure, presence of arthritis, age, weight, height, endogenous EPO level, ferritin level, predicted normal blood volume, iron deficiency, hematocrit, hemoglobin or reticulocyte count regardless of whether evaluable subjects or all subjects were used in the analyses.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Treatment with either 300 IU/kg or 100 IU/kg epoetin alfa was associated with significant ($p<\_0.05$) improvement, when compared with placebo, in the primary evaluations of efficacy.

Transfusion Requirements: Among evaluable subjects, a significantly ($p<\_0.05$) lower proportion of epoetin alfa-treated subjects (300 IU/kg, 16.7%; 100 IU/kg, 25.0%) than placebo-treated subjects (53.7%) required homologous blood transfusions during and after surgery. There was no significant difference in the proportion of subjects receiving transfusions between the 300 IU/kg and 100 IU/kg treatment groups. When the mean number of units of homologous blood transfused per subject was compared, epoetin alfa-treated subjects received significantly fewer units of blood than placebo-treated subjects (mean: 300 IU/kg, 0.37 units; 100 IU/kg, 0.58 units; placebo, 1.42 units). There was no significant difference in the mean number of units received between the 300 IU/kg and 100 IU/kg treatment groups. The results of the analysis of subjects requiring transfusions were similar whether data from the subjects evaluable for efficacy or data from all subjects (intent-to-treat) who had surgery were used.

The majority of the subjects in each treatment group had either hip (300 IU/kg - 44%, 100 IU/kg - 57%, placebo - 46%) or knee (300 IU/kg - 44%, 100 IU/kg - 31%, placebo - 42%) surgery. For subjects undergoing hip surgery, almost twice as many placebo subjects (54.8%) required homologous transfusions as did epoetin alfa-treated subjects (300 IU/kg - 25.0%, 100 IU/kg - 28.6%). For subjects undergoing knee surgery, only 12.5% of the subjects treated with 300 IU/kg of epoetin alfa required transfusions, while 28.6% of the 100 IU/kg epoetin alfa-treated and 53.6% of the placebo-treated subjects required transfusion. Among the other categories of surgery (back and other surgeries), only placebo subjects required transfusions.

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Hematology Parameters: In general, in the epoetin alfa-treated subjects, the hemoglobin and hematocrit responses paralleled each other over the course of the study. Mean hemoglobin and hematocrit increased until presurgery, decreased after surgery, remained stable the week after surgery, then increased by Week 3-4 to values somewhat below baseline. In contrast, in the placebo-treated subjects, the mean hematocrit and hemoglobin levels decreased from prestudy until Day 1 postsurgery, and stabilized for the remainder of the week after surgery. The mean hemoglobin and hematocrit levels then gradually started to increase although both levels were still below baseline levels for placebo subjects by the Week 3-4 visit.

In epoetin alfa-treated subjects, mean reticulocyte counts increased steadily through Day 1 postsurgery, then decreased slightly, and essentially returned to prestudy values by the Week 3-4 poststudy visit. Whereas in placebo-treated subjects, mean reticulocyte counts did not increase until Day 4 postsurgery at which time there was a modest increase through Weeks 2-3. During the postsurgery period, mean reticulocyte values in placebo subjects were consistently lower than those for epoetin alfa-treated subjects. This delay in reticulocyte response among placebo-treated subjects was still evident at the Week 3-4 visit.

In order to examine treatment and investigator effects upon mean changes in hematologic response over various time periods, separate two-way analyses of variance were conducted for each of these time periods. The following results are least-square (LS) means obtained from this linear model.

During the prestudy to presurgery interval there was a statistically significant positive mean change in hemoglobin for both doses of epoetin alfa (300 IU/kg, 0.7 g/dL;100 IU/kg; 0.6 g/dL) while the mean hemoglobin in the placebo group declined significantly (-0.4 g/dL). The mean change in hemoglobin was significantly greater for the 300 IU/kg and 100 IU/kg groups than that for the placebo group, while there was no significant difference between the treated groups. Similar results were noted for hematocrit.

There was a statistically significant prestudy to presurgery rise in reticulocyte count in both epoetin alfa treatment groups (300 IU/kg, 3.7 percentage points; 100 IU/kg, 3.0 percentage points). In contrast, the placebo group experienced a slight non-significant increase (0.1 percentage point). The mean change in reticulocytes was significantly greater for the 300 IU/kg and 100 IU/kg groups than that for the placebo group. The 300 IU/kg group showed a significantly greater increase over the 100 IU/kg group. There was a significant investigator effect for prestudy to presurgery reticulocyte count.

Presurgery to Day 1 postsurgery hemoglobin and hematocrit declined while reticulocyte counts rose in all three groups.

From Day 1 postsurgery to discharge, the mean reticulocyte count decreased among epoetin alfa-treated subjects. This change was statistically significant in the 300 IU/kg group. In contrast, placebo-treated subjects showed a significant increase during this time period. Although there was an increase for placebo-treated subjects, the mean reticulocyte levels for epoetin alfa-treated subjects were considerably higher than those for placebo-treated subjects during this time period. A reticulocyte response was not seen in the placebo group until Day 4 postsurgery. At the Week 3-4 poststudy visit, hematocrit and reticulocyte levels had essentially returned to baseline for 300 IU/kg-treated subjects.

Energy Assessment and Time to Discharge: There was no notable difference among the treated groups in the energy assessment parameter nor any significant difference in the mean time to hospital discharge among the three treatment groups.

SAFETY RESULTS:

Adverse Events: Of the 200 subjects enrolled, 187 (93.5%) reported adverse experiences during the study; 58 (96.7%) in the epoetin alfa 300 IU/kg group, 65 (91.6%) in the epoetin alfa 100 IU/kg group, and 64

(92.8%) in the placebo group. Comparison of either epoetin alfa treatment group with the placebo treatment group revealed statistically significant differences in the proportion of subjects reporting depression and chest pain when classified by primary term. Nine percent of the subjects in the placebo group reported depression compared to no subjects in the epoetin alfa 300 IU/kg group. Similarly, 10% of the placebo-treated subjects reported chest pain compared to one percent of the subjects in the epoetin alfa 100 IU/kg group. No other significant differences were revealed. The adverse experiences that occurred in 20% or more of subjects in either epoetin alfa-treated group were: skin reaction at medication site (300 IU/kg epoetin alfa 50.0%; 300 IU/kg epoetin alfa 46.5%), pyrexia (300 IU/kg epoetin alfa 48.30%; 300 IU/kg epoetin alfa 39.4%); skin pain (300 IU/kg epoetin alfa 45.0%; 300 IU/kg epoetin alfa 32.4%); nausea (300 IU/kg epoetin alfa 40.0%; 300 IU/kg epoetin alfa 39.4%); constipation (300 IU/kg epoetin alfa 33.3%; 300 IU/kg epoetin alfa 35.2%); insomnia (300 IU/kg epoetin alfa 26.7%; 300 IU/kg epoetin alfa 23.8%); vomiting (300 IU/kg epoetin alfa 20.0%; 300 IU/kg epoetin alfa 18.3%); headache (300 IU/kg epoetin alfa 20.0%; 300 IU/kg epoetin alfa 9.9%); and arthralgia (300 IU/kg epoetin alfa 15.0%; 300 IU/kg epoetin alfa 22.5%).

Discontinuations Due to Adverse Experiences: Twelve subjects (six 300 IU/kg epoetin alfa, four 100 IU/kg epoetin alfa, two placebo) discontinued treatment due to adverse experiences. Of these, five subjects had adverse experiences that were characterized by the investigators as possibly related to the therapy (hypertension [two subjects], hypotension, chest pain, gastritis and colitis, and chills and fever [one subject each]).

Deaths: No subject in any of the three treatment groups died while on study. One subject (#2204, placebo) died 40 days after completion of treatment, due to a motor vehicle accident. This death was not characterized by the investigator as being related to the study medication.

Safety Reports: Twelve subjects (four 300 IU/kg epoetin alfa, five 100 IU/kg epoetin alfa, three placebo) who participated in this study reported serious adverse experiences that required filing an IND Safety Report to the FDA.

Iron Stores: There were statistically significant within-treatment group decreases from baseline to last value for serum iron and TIBC in all three treatment groups but no signfficant among-treatment group differences. Differences in changes from baseline to last value among the treatment groups were statistically significant for ferritin. There was an increase in ferritin within all treatment groups, which was significant only in the placebo group. The positive mean change in ferritin levels in all treatment groups may be due to the fact that ferritin is an acute phase reactant and may increase in response to surgery or transfusions. Mean serum iron levels declined by 40.6 µg/dL in the 300 IU/kg epoetin alfa-treated group (baseline, 65.4 p.g/dL; last value, 24.8 µg/dL), 40.2 µg/dL in the 100 IU/kg epoetin alfa-treated group (baseline, 71.7 µg/dL; last value, 31.5 µg/dL) and 42.6 µg/dL in the placebo-treated group (baseline, 81.7 µg/dL; last value, 39.1 pg/dL) possibly reflecting increased erythropoiesis in all treatment groups following surgical blood loss.

Epoetin alfa Antibody Titers: All of the 200 subjects (60 300 IU/kg epoetin alfa, 71 100 IU/kg epoetin alfa, 69 placebo) had a prestudy and/or a Week 3-4 poststudy antibody determination. One subject (#605, 300 IU/kg epoetin alfa) exhibited a borderline confirmed positive titer (1:80 - 1:160) for epoetin alfa antibodies at both the pre- and poststudy assessments. Since there was no change from baseline, these titers are probably unrelated to epoetin alfa treatment. There were no other confirmed positive results.

CONCLUSIONS:

The results of this study indicate that epoetin alfa given at a dose of 300 or 100 IU/kg for ten days prior to, on the day of and four days after major orthopedic surgery results in a significantly lower incidence of exposure to

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homologous blood transfusion when compared with placebo treatment. The epoetin alfa dosing regimen was well tolerated in this subject population with a safety profile similar to that seen with placebo treatment.		

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