SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: EPREX®, ERYPO® (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)

Protocol No.: EPO-C111-457/EPO-INT-10

Title of Study: A Double-Blind, Placebo-Controlled Study to Assess the Effect of Early Intervention and/or Treatment with Epoetin Alfa on Anemia in Cancer Patients Receiving Non-Platinum Containing Chemotherapy

Investigators: 73 investigators.

Study Centre(s): 73 centers in 15 countries.

Publication (Reference): None

Studied Period (years): 29 July 1996 through 13 August 1998 | **Phase of development:** 3

Objectives: The purpose of this study was 1) to assess the effect of early intervention or treatment with epoetin alfa on transfusion requirements and anemia in subjects receiving non-platinum-containing chemotherapy for non-myeloid malignancies; 2) to establish whether changes in erythropoietin and hemoglobin levels after two weeks, serum ferritin levels after two weeks, changes in hemoglobin levels and reticulocyte counts after either two or four weeks predict responsiveness to epoetin alfa therapy; and 3) to assess the benefits on quality of life, particularly fatigue, associated with the use of epoetin alfa.

Methodology: This trial was a multicenter, randomized, double-blind, placebo-controlled study conducted in 15 countries. To enroll subjects thought to be at high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects who had either low baseline hemoglobin levels (≤10.5 g/dL) at any time during chemotherapy or to those subjects whose hemoglobin had fallen substantially (≥1.5 g/dL per cycle or per month) since the beginning of the current course of chemotherapy such that it dropped to ≤12 g/dL. Subjects were stratified by tumor type (solid vs hematological) and hemoglobin level (≤10.5 g/dL and >10.5 g/dL). Treatment was to continue for 12 to 24 weeks (or three to six chemotherapy cycles), plus four weeks post-chemotherapy.

Number of Subjects (planned and analyzed): 360 planned; 375 analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were to be ≥18 years old, with a confirmed diagnosis of non-myeloid malignancy for which non-platinum-containing chemotherapy was underway or imminent, with a performance score (ECOG) of 0, 1, 2, or 3 (i.e., not completely disabled) and a life expectancy of at least six months, and with a baseline hemoglobin ≤10.5 g/dL, or a fall in hemoglobin level ≥1.5 g/dL per cycle or per month since the beginning of the current course of chemotherapy such that it dropped to ≤12.0 g/dL. Subjects were not to have been previously treated by platinum-containing chemotherapy for ≥3 months.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (EPREX® or ERYPO®) at 150 IU/kg, s.c., t.i.w.; if, after four weeks of therapy, a subject's reticulocyte count increased <40,000/μL above baseline or the hemoglobin level increased by less than 1 g/dL above baseline, the initial dose (150 IU/kg t.i.w.) was to be doubled to 300 IU/kg t.i.w. Batch Nos. 5M608T, 6D617T, 6E606T, 6J619T, 6M603T for the 10,000 IU/mL syringes; and 5L603T, 6E609T, 6G625T, 6J617T, 6M616T, 7E621T for the 4,000 IU/ 0.4 mL syringes.

Duration of Treatment: 12 to 24 weeks or three to six chemotherapy cycles, plus four weeks post-chemotherapy.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, s.c., t.i.w.; Batch Nos. 901511, 909607, 901704 for the 10,000 IU/mL syringes; and 902511, 910607, 902610 for the 4,000 IU/ 0.4 mL syringes.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy: Efficacy evaluations were based on comparisons between treatment groups of the effectiveness of early intervention or treatment with epoetin alfa on anemia in cancer subjects undergoing non-platinum containing chemotherapy. Primary efficacy evaluations were based on transfusion requirements. Secondary evaluations included changes in hemoglobin levels, hematocrit levels, reticulocyte counts, predictive algorithms for response, and quality-of-life parameters. Safety: Safety evaluations included assessments of the incidence and severity of adverse events, clinical laboratory tests, vital sign measurements, and physical examinations.

Statistical Methods: The proportion of subjects transfused after the first four weeks of treatment was the main focus of the analysis. Subjects who were on study for ≤28 days were counted as transfused for the intent-to-treat analysis. The efficacy population included all subjects who were in the study for >28 days. A logistic regression model was used, including terms for the main effects of treatment group, primary tumor type (solid vs. hematologic), hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL), and interaction terms for treatment by tumor type and treatment by hemoglobin stratum. Secondary efficacy variables included the proportion of subjects transfused or with a hemoglobin level below 8 g/dL; cumulative transfusion rate relative to the observation period excluding the first month; time to first transfusion or hemoglobin level <8 g/dL after the first month; the proportion of correctors, responders, and final response (each unrelated to transfusions); change of hemoglobin level, hematocrit level, and reticulocyte count from baseline to final visit; change in the performance status from baseline to the last value on study; and quality-of-life assessments.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The efficacy of epoetin alfa in treated subjects with anemia has been demonstrated in that the proportion of subjects transfused after Day 28 was significantly smaller in the epoetin alfa-treated group than in the placebo-treated group (p=0.0057, intent-to-treat; p=0.0168, efficacy). The proportion of subjects transfused after Day 28, regardless of the tumor type (solid or hematological) or baseline hemoglobin level (≤10.5 g/dL or >10.5 g/dL), was greater in the placebo group than in the epoetin alfa group. The logistic regression results with treatment group, tumor type, and hemoglobin stratum as covariates showed that the relationship between tumor type and the proportion of subjects transfused after Day 28 was not statistically significant for either the intent-to-treat (p=0.43) or efficacy (p=0.19) populations. The effect of hemoglobin stratum as a covariate was statistically significant for both the intent-to-treat (p=0.0017) and efficacy (p=0.0022) populations.

Proportion of Subjects Transfused After Day 28 by Subgroup (Protocol EPO-C111-457/EPO-INT-10)

	Epoetin Alfa		Placebo	
Subgroup	N	%	N	%
Intent-to-Treat Population	**(N=251)**		**(N=124)**	
Tumor Type: Solid	33/136	(24.3%)	24/66	(36.4%)
Hematologic	29/115	(25.2%)	25/58	(43.1%)
Hemoglobin Level: ≤10.5 g/dL	59/209	(28.2%)	46/109	(42.2%)
>10.5 g/dL	3/42	(7.1%)	3/15	(20.0%)

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EFFICACY RESULTS (continued):

The effect of epoetin alfa was also clearly demonstrated by significantly greater increases in hemoglobin and hematocrit ($p<0.001$) and in reticulocyte counts ($p=0.037$) from baseline to last visit compared with placebo, and by significantly more responders (≥2 g/dL hemoglobin change from baseline) and correctors(reached hemoglobin ≥12 g/dL) unrelated to transfusions. For subjects stratified to the >10.5 g/dL hemoglobin level, mean hemoglobin levels were maintained or increased between Weeks 2 and 16 in the epoetin alfa group compared with the placebo group, indicating that early treatment with epoetin alfa can prevent anemia requiring transfusion. At last assessment, the analysis of the change scores calculated between baseline and last assessment for five of the seven primary quality-of-life scales (the Total FACT-G, the FACT-An Fatigue, and the three CLAS scales), showed significant advantages for subjects randomized to epoetin alfa compared with placebo. A strong, positive association was found between the seven primary quality-of-life scale scores and hemoglobin levels, as well as strong associations between changes in hemoglobin levels and quality-of-life scores. Although the study was not designed with mortality as an endpoint, overall Kaplan-Meier estimates of survival measured up to three months after the last subject completed the study, showed a statistically significant result in favor of the epoetin alfa-treated group. The estimated median survival duration was 16.8 months for the epoetin alfa-treated group and 10.7 months for the placebo group. The estimated hazard ration was 1.38 (95% CI 1.03 to 1.85) indicating that the risk of death for placebo-treated subjects is 1.38 times the risk of death for epoetin alfa-treated subjects. Survival by tumor type was consistent with overall findings showing a trend in favor of the epoetin alfa-treated group.

SAFETY RESULTS: Overall, treatment with epoetin alfa did not result in adverse events that were unexpected for a population of subjects with cancer who were undergoing chemotherapy. The incidence of adverse events was similar between the epoetin alfa and placebo groups with the most frequently reported adverse events being fever, aggravated malignant neoplasm, nausea, granulocytopenia, constipation, leukopenia, and abdominal pain. The incidence of serious adverse events (34% epoetin alfa, 36% placebo) and discontinuations due to adverse events (15% epoetin alfa, 15% placebo) was also similar between the two treatment groups, and the incidence of deaths was slightly lower in the epoetin alfa group compared with the placebo group (14% epoetin alfa, 18% placebo). The response to chemotherapy was similar between the treatment groups.

CONCLUSION: Epoetin alfa at a dose of 150 IU/kg t.i.w. demonstrated effectiveness in treating anemia by lower transfusion requirements and greater increases in hematopoietic variables when compared with placebo. Quality-of-life data support a strong treatment effect for epoetin alfa on cancer-specific quality-of-life domains, consistent with a mechanism of action mediated by and increase in hemoglobin levels. There was a statistically significant survival result in favor of epoetin alfa where the median survival was 6.1 months longer in the epoetin alfa-treated group compared with placebo. Treatment with epoetin alfa was safe and well tolerated in a population of subjects who were receiving non-platinum-containing chemotherapy for non-myeloid malignancies (including both solid and hematological malignancies).

Date of the report: 12 March 1999