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.: CR005923 **Title of Study:** A Placebo Controlled Study on the Effect of r-HuEPO in Patients with Malignancy Receiving Chemotherapy		
Investigators: 28 investigators.		
Study Centre(s): 28 centers in 4 countries.		
Publication (Reference): None		
Studied Period (years): 7 February 1995 through 14 May 1998		**Phase of development:** 3
Objectives: The purpose of this study was to compare the ability of epoetin alfa and placebo to prevent transfusion, to treat or prevent anemia, and to investigate quality-of-life benefits associated with the use of epoetin alfa in subjects receiving chemotherapy for selected malignancies.		
Methodology: This trial was a multicenter, double-blind, placebo-controlled study conducted in four countries, followed by an open-label extension. To enroll subjects thought to be a high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects whose hemoglobin had fallen substantially (≥1.5 g/dL) since the beginning of the current course of chemotherapy or who had a baseline hemoglobin level <12 g/dL and who were predicted to receive chemotherapy for at least three more months. Treatment was to continue for 12 weeks. Subjects who completed the 12-week double-blind portion of the study were eligible to receive epoetin alfa for an additional 12 weeks in an open-label extension to the study.		
Number of Subjects (planned and analyzed): 201 planned and analyzed.		
Diagnosis and Main Criteria for Inclusion: Subjects were to be between 18 and 80 years old, with a confirmed diagnosis of one of the following: multiple myeloma, lymphoma, breast cancer, ovarian cancer, small-cell lung cancer, esophagus cancer, or prostate cancer. Chemotherapy was to be currently underway or imminent, and subjects were to have a hemoglobin level <12 g/dL or a hemoglobin decline of ≥1.5 g/dL during the current cycle of chemotherapy, 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. Subjects were not to be receiving concomitant continuous use of anabolic steroid therapy.		
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 hemoglobin had 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. 4D226T, 4E216T, 5A202T, 5L206T, 6B227T, 6D226T, 6J217T.		
Duration of Treatment: 12 week double-blind phase; subjects who completed the 12-week double-blind phase were eligible to receive epoetin alfa for an additional 12 weeks in an open-label extension to the study.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, s.c., t.i.w.; Batch Nos. 903401 and 5F001T.		

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Efficacy: Double-blind 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 chemotherapy. Primary efficacy evaluations were based on transfusion requirements. Secondary evaluations were based on changes in hemoglobin levels, reticulocyte counts, the number of responders or correctors, cumulative transfusion rate, change in performance score, physician's global assessment, and quality of life. Open-label summaries included discontinuation/completion information, course of mean dosing during double-blind and open-label phases, and mean weekly hemoglobin levels during double-blind and open-label phases. 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 in the intent-to-treat population during Months 2 or 3 of the double-blind phase was the main focus of the analysis. For this population, the analysis counted subjects who were on study for ≤28 days as transfused. The analysis was carried out using a logistic regression model that included terms for the main effects of treatment group, primary tumor types (solid vs. hematological), and interaction term for treatment by tumor type. The efficacy population (all subjects in the study >28 days) was used for analysis of the secondary efficacy variables. A separate subgroup presentation of the proportion of subjects transfused during Months 2 and 3 of the double-blind phase was analyzed overall and presented stratified by 1) subjects with nonplatinum vs. platinum chemotherapy, 2) tumor type (solid vs. hematological), and 3) subject prestudy transfusion dependence. Additional secondary variables included change in hematopoietic variables (hemoglobin and reticulocytes) from baseline to final visit, the number of subjects achieving an increase in hemoglobin (unrelated to transfusion) of ≥2 g/dL from baseline (responder) or achieving an absolute hemoglobin (unrelated to transfusion) of ≥12 g/dL (corrector), cumulative transfusion rate, change in performance score, the physician's global assessment, and quality of life.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The efficacy of epoetin alfa in treating subjects with anemia has been demonstrated in that the proportion of subjects transfused during Months 2 or 3 was significantly smaller in the epoetin alfa-treated group than in the placebo-treated group ($p=0.0018$, intent-to-treat; $p=0.0003$, efficacy). The proportion of subjects transfused during Months 2 or 3, regardless of tumor type (solid or hematological), type of chemotherapy (platinum or non-platinum), or baseline transfusion dependency was greater in the placebo group than in the epoetin alfa group.

The effect of epoetin alfa was also clearly demonstrated by significantly greater increases in hemoglobin level ($p=0.0001$) from baseline to last value compared with placebo, and by significantly more responders ($p<0.001$) and correctors ($p<0.001$) unrelated to transfusions. Performance score indicated an improvement in condition in a higher proportion epoetin alfa-treated subjects compared with placebo, and physician's global assessment was significantly ($p<0.001$) better in subjects administered epoetin alfa. At Week 12 quality-of-life assessments, there was significant improvement in Fatigue scales in epoetin alfa-treated subjects, and a significant decline in Physical Functioning in placebo-treated subjects with hematological malignancies. A strong correlation was found between hemoglobin and all of the quality-of-life domains of interest. In the open-label phase of the study, increases in hemoglobin levels and improvements in physician's global assessments were observed among subjects who were administered placebo during the double-blind phase of the study and epoetin alfa during the open-label phase ("formerly placebo"). Maintenance of hemoglobin and continued improvement in physician's global assessment was observed among subjects who remained on epoetin alfa during the open-label phase of the study ("formerly epoetin alfa").

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EFFICACY RESULTS (continued):

Proportion of Subjects Transfused During Months 2 or 3 (Protocol CR005923)

	Epoetin Alfa N	(%)	Placebo N	(%)
Intent-to-Treat Population	**(N=136)**		**(N=65)**	
	21	(15.4%)	23	(35.4%)
Efficacy Population	**(N=108)**		**(N=57)**	
	10	(9.3%)	19	(33.3%)
Type of Chemotherapy:				
Platinum	3/29	(10.3%)	9/15	(60.0%)
Non-platinum	7/79	(8.9%)	10/42	(23.8%)
Tumor Type: Solid	6/68	(8.8%)	15/37	(40.5%)
Hematological	4/40	(10.0%)	4/20	(20.0%)
Baseline Transfusion Dependence:				
Transfusion Dependent	6/29	(20.7%)	5/9	(55.6%)
Transfusion Independent	4/79	(5.1%)	14/48	(29.2%)

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 (59%) and placebo (65%) groups; the most frequently reported adverse events were fever, fatigue, nausea, and aggravated malignant neoplasm. The incidence of serious adverse events (26% epoetin alfa, 29% placebo) was similar between the two groups and discontinuations due to adverse events (11% epoetin alfa, 5% placebo) was slightly higher in the epoetin alfa group. The incidence of deaths was 6% in the epoetin alfa group and 5% in the placebo group. The response to chemotherapy was similar between the treatment groups. In the open-label phase of the study, there were no notable differences between groups with regard to the incidence of treatment-emergent adverse and serious adverse events; aggravated malignant neoplasm was the most frequently reported serious adverse event in both groups. There were slightly more deaths (16%) in the "formerly placebo" group compared with the "formerly epoetin alfa" group (9%), and slightly more discontinuations due to adverse events (16%) in the "formerly placebo" group compared with the "formerly epoetin alfa" group (9%).

CONCLUSION: The efficacy of epoetin alfa 150 to 300 IU/kg in subjects receiving chemotherapy for solid and hematologic malignancies was clearly demonstrated by fewer transfusion requirements, greater increases in hemoglobin levels, and higher proportions of responders and correctors. Transfusion requirements were reduced regardless of the type of chemotherapy, tumor type, or prestudy transfusion dependence. Overall, epoetin alfa was safe and well tolerated in a population of subjects who were receiving chemotherapy for malignancies.

Date of the report: 12 March 1999

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