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.: CR005911
Title of Study: A Placebo-Controlled Study On The Effect of Epoetin Alfa in Subjects with Multiple Myeloma Followed by an Open-Label Extension

Investigators: 31 investigators.

Study Center(s): 31 study centers in 12 countries.

Publication (Reference): Dammacco F. XIVth Meeting of the International Society of Haematology Oral Session 10. 1997;O-046;49; Dammacco F. Eur J Cancer 1997;33(Suppl.8):394; Dammacco F, Castoldi G, Roedjer S. Blood 1997;90(Suppl.1):358a.

Studied Period (years): February 17, 1994 - October 10, 1996 | **Phase of development**: 3

Objectives: To compare the ability of epoetin alfa and placebo in preventing transfusions or anemia in subjects with multiple myeloma, and to investigate quality-of-life benefits associated with the use of epoetin alfa.

Methodology: This trial was a multicenter, double-blind, placebo-controlled study conducted in 12 countries, followed by an open-label extension. To enroll subjects thought to be at high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects who had a low baseline hemoglobin value and who had received chemotherapy starting at least six months previously. Subjects were stratified into two groups depending on whether or not they received at least one blood transfusion within the previous three months. If, after four weeks of therapy, a subject's hemoglobin level had increased by less than 1 g/dL above baseline, the initial dose (150 IU/kg t.i.w.) was to be adjusted to 300 IU/kg t.i.w. Treatment was to continue for 12 weeks. All subjects who completed this 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): 134 planned; 145 analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects, 40 to 80 years old, with documented multiple myeloma, with a performance score (ECOG) of 0, 1, 2, or 3 (i.e., not completely disabled) and a life expectancy of at least three months, and with a baseline hemoglobin <11 g/dL and baseline reticulocyte count <100,000/µL. At least six months were to have elapsed since the beginning of chemotherapy.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (EPREX® or ERYPO®) at 150 IU/kg, s.c. t.i.w.; Batch Nos. 3H517T, 3M516T, 4B518T, 4C207T, 4D226T, 4E216T, 5A202T, 5H221T, 5K230T, 5L206T, 5M511T, 6B227T, and 6D226T.

Duration of Treatment: 12 weeks for the double-blind phase, and 12 weeks for the open-label extension.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, s.c. t.i.w.; Batch Nos. 5F001T, 903401, and 923301.

Criteria for Evaluation:

Efficacy: Efficacy evaluations were based on comparisons between treatment groups of transfusion requirements (proportion of subjects transfused and number of units transfused) during the study stratified by baseline transfusion status, on the number of subjects whose hemoglobin level reached at least 12 g/dL (correctors) or had an increase in hemoglobin of at least 2 g/dL (responders), and on changes in 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. Serum and urine M-protein levels were compared for changes in underlying disease.

SYNOPSIS (CONTINUED)

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Statistical Methods: The proportion of subjects transfused during Months 2 or 3 was the main focus of the analysis. The Cochran-Mantel-Haenszel test was used to compare the proportion of subjects transfused stratified by prestudy transfusion dependence. Secondary efficacy variables included additional transfusion variables, changes in hemoglobin and hematocrit levels, reticulocyte counts, and serum erythropoietin levels, proportions of correctors and responders, quality-of-life assessments, performance score, and the physician's global assessment.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The efficacy of epoetin alfa in treating subjects with multiple myeloma has been demonstrated in that the proportion of subjects transfused was significantly smaller in the epoetin alfa-treated group than in the placebo-treated group ($p=0.028$ for the efficacy population and $p=0.006$ for the intent-to-treat population, stratifying by prestudy transfusion dependence).

Proportion of Subjects Transfused During Months 2 or 3 of Double-Blind Phase, by Prestudy Transfusion Dependence (Efficacy Population) (Protocol CR005911)

Transfused Placebo Prestudy	Transfused During Months 2 or 3	150 IU/kg Epoetin Alfa N (%)		Placebo N (%)		p-Valuea
		(N=66)		(N=66)		0.028
Yes	Yes	12	(52.2)	16	(72.7)	
	No	11	(47.8)	6	(27.3)	
No	Yes	4	(9.3)	10	(22.7)	
	No	39	(90.7)	34	(77.3)	

a Cochran-Mantel Haenszel test, comparing the proportions of subjects transfused stratified by prestudy transfusion dependence.

The effect of epoetin alfa was also clearly demonstrated by significantly greater increases in hemoglobin and hematocrit ($p<0.001$) and in reticulocyte counts ($p=0.025$) from baseline to last value compared with placebo, and by significantly more correctors (hemoglobin ≥12 g/dL reached) and responders (≥2 g/dL hemoglobin change from baseline) unrelated to transfusions ($p<0.001$). No significant differences were observed with regard to Week 12 change in quality-of-life scores. However, many more of the quality-of-life subscales showed significant improvement within the epoetin alfa-treated group than within the placebo-treated group. Significant improvements in change of performance scores based on investigator assessment were observed in the epoetin alfa-treated group compared with the placebo-treated group ($p=0.038$). Increases in hemoglobin levels and improvements in quality of life were generally observed among subjects who switched from placebo during the double-blind phase to epoetin alfa during the open-label phase, while maintenance of both hemoglobin levels and quality of life was observed among subjects who remained on epoetin alfa.

SAFETY RESULTS: Overall, epoetin alfa was safe and well tolerated. Treatment-emergent adverse events were similar among treatment groups. Fever, leucopenia, and pain were the most frequently reported adverse events. Similar proportions of subjects (2.9% epoetin alfa-treated and 3.9% placebo-treated) discontinued treatment due to one or more adverse events. More placebo-treated subjects than epoetin alfa-treated subjects died (seven vs. one, respectively) and more placebo-treated subjects than epoetin alfa-treated subjects discontinued treatment due to disease progression (six vs. none, respectively) despite similar multiple myeloma disease staging at baseline and at the end of the study. Thus, epoetin alfa had no negative effect on disease progression. Serious adverse events were in general similarly distributed both across body systems and between treatment groups. There were no noteworthy differences between treatment groups in clinical laboratory test results, vital sign measurements, or other physical findings. As expected, mean iron stores decreased in epoetin alfa-treated subjects compared with placebo, reflective of the utilization of iron stores during enhanced erythropoiesis.

CONCLUSION: Epoetin alfa was safe and well tolerated in a multiple myeloma subject population, and there were no negative effects on disease progression. The efficacy of epoetin alfa was clearly demonstrated by lesser transfusion requirements and greater increases in erythropoietin parameters (hemoglobin levels, hematocrit levels, and reticulocyte counts) when compared with placebo.

Date of the report: 16 June 1998

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