NAME OF COMPANY	PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
Cilag Trademarks: EPREX® Name of active ingredients: Recombinant-human Erythropoietin (r-HuEPO)	Part: IVB Protocol 87-020 Volume:	

Title of the Study: A Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of r-HuEPO in AIDS Patients With Anemia Induced by Their Disease and AZT Therapy

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Study Center: Multicenter

Clinical Phase: II

Objective: To determine the safety and efficacy of r-HuEPO administered subcutaneously to AIDS patients with anaemia secondary to their disease and/or concomitant AZT Therapy

Study Design: Double-blind, parallel group, placebo-controlled, randomized study in which 60 patients were enrolled and randomly assigned one of two treatment groups: Group 1 received r-HuEPO subcutaneously for 12 weeks and Group 2 received placebo subcutaneously for 12 weeks

Number of Patients: 60 patients (r-HuEPO=30 ; placebo=30)

Dosage and Admin.: 100 U/Kg, s.c., 3x/week

Duration of Treatment: 12 weeks or until the haematocrit rose to 38%, whichever occurred first

Criteria for Evaluation: The effect of therapy on the number of patients who achieved the target haematocrit, on transfusion requirements (number of patients transfused per month, number of units transfused per patient per month), haematocrit (and haemoglobin) levels, physicians' global evaluation and well being assessments were evaluated.

Summary: Patients receiving r-HuEPO therapy experienced a statistically significant increase from baseline to endpoint in haematocrit (3.76 percentage points), however for placebo-treated patients this was not true (increase of 1.62 percentage points). Although the changes in transfusion requirements from baseline to end of double-blind treatment were not statistically significant, there was a trend toward a greater increase in the total number of units transfused during the three months of treatment for placebo-treated patients than for r-HuEPO-treated patients. The mean number of units transfused per r-HuEPO-treated patients during three months of double-blind therapy was 4.64 units, a 16.3% increase from baseline transfusion

requirements compared to a mean of 5.79 units for placebo-treated patients an increase of 69.3% from baseline requirements. For low EPO, r-HuEPO-treated patients, the mean number of units transfused was 3.76 units, a 6.2% increase from baseline; for low EPO, placebo-treated patients, 5.04 units were transfused a 64.7% increase.

There was no statistically significant differences between treatment groups in Physician's Global Evaluation or the Well Being Assessment.

Safety:

Twenty-eight r-HuEPO-treated patients (93%) and 28 placebo-treated patients (93%) reported adverse experiences during the study. The most common types of adverse experiences observed in this study are as follows: asthenia, pyrexia, fatigue, nausea,vomiting, cough, diarrhea, shortness of breath, and respiratory congestion. The only statistically significant difference between treatment groups occurred in the number of patients reporting sinusitis during the double-blind phase of the study (5 r-HuEPO patients vs 0 placebo patients). These adverse experiences along with the others reported during the study appeared to be related to the disease process of AIDS and are thought to be unrelated to r-HuEPO or placebo therapy.

Two r-HuEPO patients discontinued double-blind treatment due to adverse experiences, one patient had cytomegalovirus infection, the other patient discontinued due to fatigue which later resulted in death due to aspiration (this one death, mentioned above, was the only one reported). There were eight reports (four r-HuEPO, four placebo) of AIDS-defining opportunistic infection in this double-blind study. These were probably associated with the progression of the disease (AIDS) and are not thought to be treatment-related.

Conclusions:

The results of this study indicate that r-HuEPO administered subcutaneously at a dose of 100 U/Kg three-times-a-week for twelve weeks increases haematocrit from baseline to last value in anaemic AZT-treated AIDS patients, the mean change in hematocrit from baseline to endpoint was not statistically significant for placebo-treated patients. The difference between the r-HuEPO treatment group and the placebo treatment group in the change in haematocrit from baseline to last value did not achieve statistical significance. Low endogenous EPO, r-HuEPO-treated patients exhibited a trend toward a greater increase in mean haematocrit compared to low EPO, placebo-treated patients, even though low EPO, r-HuEPO-treated patients experienced a 25% reduction in cumulative transfusion requirements during double-blind therapy relative to low EPO, placebo patients. Treatment with r-HuEPO at a dose of 100 U/Kg did not show statistically significant effects on other efficacy parameters evaluated (transfusion requirements, number of patients achieving the target haematocrit, Physician's Global Evaluations and Well-Being assessments).

TABLE 1

Name of Company: Cilag Name of Finished Product: EPREX® Name of Active Ingredients: Recombinant Human Erythropoietin (r-HuEPO)				Summary of Clinical Trials referred to Part IV B of the dossier I. PARALLEL DOUBLE BLIND STUDY			(For National Authority Use Only)		
Ref. Volume	Study	Design	No. of Subjects	Diagnosis	Duration of Treatment	Dosage Regimen Route of Admin.	Criteria for Evaluation	Results (Efficacy)	Adverse Reactions
	Multi-Center Protocol 87-020	Double-Blind Placebo-Controlled Randomized Parallel Study	60 Group 1: r-HuEPO 30 pts 29(M), 1(F) 26-61 years old Group 2: Placebo 30 pts 28(M),2(F) 28-55 years old	AIDS Patients with Anaemia Induced by Their Disease and AZT Therapy	12 weeks or until the haematocrit rose to 38%	Group 1: 100 U/kg r-HuEPO s.c. 3x/week Group 2: Placebo s.c. 3x/week	The effects of drug vs placebo on haematocrit, haemoglobin and transfusion requirements Comparison of the number of patients who achieved the target haematocrit (38-40%), unrelated to transfusion or AZT dose reduction Comparison of the patients Well Being Assessment and Physicians' Global Evaluation	All patients receiving r-HuEPO experienced a stat. sign. mean increase from baseline to endpoint in hct (p=0.027, 3.76 percentage points). The increase in hct in low EPO patients was not stat. sign. (p=0.115). Placebo pts mean change was not statistically sign. (p=0.136, 1.62%). The difference between treatment groups in mean change in hct/hgb were not stat. sign. for all patients (p=0.273). The mean number of units transfused per r-HuEPO-treated pts during 3 months of therapy was 4.64 units, 16.3% increase from baseline vs 5.79 units for placebo-treated pts, an increase of 69.3% from baseline requirements. For low EPO, r-HuEPO treated pts, the mean number of units transfused was 3.76 units, a 6.2% increase from baseline, for low EPO, placebo-treated pts, 5.04 units were transfused, a 64.7% increase. There was no statistically sign. differences between groups in the Physicians' Global Evaluation or the Well Being Assessment.	≥20% in either group: Asthenia Pyrexia Fatigue Nausea Vomiting Diarrhea Oral Candidiasis Dizziness Headache Weight Loss Shortness of Breath Cough Respiratory Congestion Discontinued due to adverse exp: N=2 Deaths: N=1

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