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 I88-009 Volume:	

Title of the Study: A Double-Blind, Placebo-Controlled Study to Determine the Safety and Efficacy of Subcutaneous Doses 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 102 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: 102 patients (r-HuEPO=51 ; placebo=51)

Dosage and Admin.: 150 U/Kg, s.c., 3x/week

Duration of Treatment: 12 weeks

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, physician global evaluations and well being assessments were evaluated.

Summary: Benefits of r-HuEPo therapy in terms of reduced transfusion requirements and increased hct were most apparent in patients with endogenous EPO levels of $\leq$500 mU/ml.

Transfusion requirements were significantly reduced by two months in r-HuEPO-treated patients with endogenous levels less than or equal to 500 mU/ml (low EPO). By the end of two months of therapy, 22% of low EPO, r-HuEPO-treated patients required transfusions compared to 59% for placebo-treated patients. Low EPO, r-HuEPO-treated patients required 0.78 units per patient per month versus 2.09 units per patient per month for placebo-treated patients. A breakdown of patients by transfusion status at baseline indicated that the low EPO patients who were transfusion dependent at baseline benefitted most from r-HuEPO therapy.

The reduction of transfusion requirements in patients with low endogenous EPO levels was reflected in the number of responders in r-HuEPO-treated patients. Seven of the eight responders (those patients attaining a haematocrit of 38% without transfusion or a significant reduction of AZT dose) in the r-HuEPO-treated group had low endogenous EPO levels.

Treatment with r-HuEPO was also associated with a statistically significant increase in the mean change from baseline to last visit in haematocrit when compared to placebo therapy for all patients regardless of endogenous EPO level. Finally, r-HuEPO therapy in low EPO patients was associated with a statistically significantly better distribution in the Physician's Global Evaluation of study medication when compared to placebo therapy in low EPO patients.

Safety:

Forty-three r-HuEPO-treated patients (84%) and 44 placebo-treated patients (86%) reported adverse experiences during the study. The most common types of adverse experiences observed in this study were as follows: pyrexia and fatigue. 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 patients discontinued double-blind treatment due to adverse experiences. Both belonged to the low EPO, r-HuEPO treated group, one discontinued due to septic shock, the other due to pneumocystis pneumonia. Three deaths were reported, all three deaths occurred in low EPO, r-HuEPO-treated patients. The two patients that discontinued eventually died, the third death was due to cardiopulmonary arrest. None of these deaths were characterized by the investigator to be drug related.

There were six reports (five r-HuEPO, one 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, given at a dose of 150 U/Kg, s.c., three-times-a-week can significantly reduce anaemia in r-HuEPO-treated patients with baseline serum endogenous erythropoietin levels less than or equal to 500 mU/mL. A reduction in transfusion requirements, an increase in mean haematocrit and an increase in the proportion of patients attaining the target haematocrit (38%) compared to placebo-treated patients were observed. This dosing regimen and route of administration is well tolerated in this

population of patients with there being no increase in adverse experiences over that seen with placebo therapy.

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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 I88-009	Double-Blind Placebo-Controlled Parallel Study	102 Group 1: r-HuEPO 51 pts 50 (M),1(F) 25-62 years old Group 2: Placebo 51 pts 49(M),2(F) 25-62 years old	AIDS Patients with Anaemia Induced by Their Disease and AZT Therapy	12 weeks or until a haematocrit of 38-40% was achieved	Group 1: 150 U/kg r-HuEPO s.c. 3x/week Group 2: Placebo s.c. 3x/week	The effects of r-HuEPO vs placebo on haematocrit, haemoglobin, and transfusion requirements *The number* of patients who achieved the target haematocrit (38-40%), unrelated to transfusion or AZT dose reduction The patients *Well Being* Assessment and Physicians' Global Evaluation.	8 of the 44 r-HuEPO-treated patients responded to therapy by attaining a hct. of 38% without transfusion or sign. reduction of AZT (7 were in the low EPO grp, one in the high EPO group and 0 in the placebo group. By Month 2, 22% low EPO, r-HuEPO treated patients required transfusions vs 59% for placebo treated patients. At *endpoint*, 33% *r-HuEPO pts vs 64% placebo pts* required transfusions. By the end of 2 months, low EPO,r-HuEPO treated pts required 0.78 units/pts/month vs 2.09 units/pts/month for placebo-treated pts Treatment with r-HuEPO was associated with a statistically sign. increase in the mean change from baseline to last visit in hct and hgb when compared to placebo therapy for all patients ($p \leq 0.05$) *r-HuEPO therapy* was associated with a statistically sign. better distribution in the Physicians' Global Evaluation for low EPO, r-HuEPO pts than for low EPO, placebo pts.	≥20% in either group: Pyrexia Fatigue Discontinued due to adverse exp: N=2 Deaths: N=3

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