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 87-021 Volume:	

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

Authors: D.A. Saad, M.S.; K.A. McCarroll, Ph.D.; K.G. Twichell, A.B.

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 72 patients were enrolled and randomly assigned one of two treatment groups: Group 1 received r-HuEPO subcutaneously for 12 weeks or until the haematocrit rose to 38%, whichever came first and Group 2 received placebo subcutaneously for 12 weeks. All patients completing this phase were eligible to enter an open-label phase of the study in which patients were given subcutaneous r-HuEPO for six months at a dose titrated to maintain the haematocrit between 38 and 40%.

Number of Patients: 72 patients (r-HuEPO=34 ; placebo=38)

Dosage and Admin.: 200 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, transfusion requirements (number of patients transfused per month, number of units transfused per patient per month), haematocrit (and haemoglobin) levels, physician global evaluations and quality of life assessments was evaluated.

Summary: Benefit of r-HuEPO therapy in terms of reduced transfusion requirements, increased hct and hgb and achieving the target hct without transfusion or AZT dose reduction was most apparent in patients with endogenous EPO levels of $\leq$500 mU/ml.

By the end of three months of therapy, transfusion requirements in r-HuEPO-treated patients were reduced; 33% of r-HuEPO-treated patients required transfusions, compared to 60% of placebo-treated patients. In addition, r-HuEPO patients required fewer units transfused (1.14 units) during the third month of therapy than did placebo-treated patients (2.08 units). Treatment with r-HuEPO was associated with statistically significant mean increases from baseline to last visit in both haematocrit and haemoglobin when compared to placebo for patients with low endogenous EPO levels. The reduction in transfusion requirements and the increase in haematocrit and haemoglobin in patients with low endogenous EPO levels were reflected in the number of r-HuEPO-treated responders. Overall, 25% of the patients in the low EPO group responded to r-HuEPO therapy versus none in the placebo group.

There were no statistically significant differences between treatment groups in the Physicians' Global Evaluation of study medication or in the Patient's Well Being Assessment.

Safety:

Thirty-one r-HuEPO-treated patients (91.2%) and 35 placebo-treated patients (92.1%) reported adverse experiences during double-blind therapy. The most frequently reported adverse experiences were pyrexia, fatigue, headache, skin reaction at the medication site, nausea and diaphoresis.

Six patients (3 r-HuEPO, 3 placebo) discontinued double-blind due to adverse experiences, these were, nausea, hand discomfort, and confusion (placebo); cytomegalovirus retinitis (r-HuEPO); flu like symptoms and decreased WBC and platelets (placebo); rash (r-HuEPO); confusion, depression (r-HuEPO); and pneumocystis carinii pneumonia (placebo). Six r-HuEPO patients developed AIDS-defining opportunistic infection during the double-blind phase of the study. These infections were probably associated with the progression of the disease and were not thought to be treatment-related.

Conclusions:

The results of this study indicate that r-HuEPO administered subcutaneously at a dose of 200 U/Kg three times-a-week for twelve weeks can significantly improve anaemia in r-HuEPO-treated AIDS patients compared to patients treated with placebo. Improvement was determined by change in haematocrit, haemoglobin, transfusion requirements and in the proportion of patients achieving the target haematocrit (38%) without a transfusion and without a significant reduction in AZT dose. This improvement was most apparent in patients with an endogenous serum erythropoietin level $\leq$ 500 mU/mL; this group of patients experienced statistically significant increases in haematocrit and haemoglobin, a reduction in number of units transfused during the third month of treatment which approached, but did not achieve, statistical significance, and a statistically significantly greater proportion of responders than the low EPO, placebo-treated group.

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 87-021	Double-Blind Placebo-Controlled Randomized Parallel Study	72 Group 1: r-HuEPO 34 pts 33(M),1(F) 26-64 years old Group 2: Placebo 38 pts 36(M),2(F) 24-56 years old	AIDS Patients with Anaemia Induced by Their Disease and AZT Therapy	12 weeks or until the haematocrit rose to 38%	Group 1: 200 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 The number of patients who achieved the target haematocrit (38-40%) The patients Well Being Assessment and Physicians' Global Evaluation	By the end of 3 months, 33% of r-HuEPO-treated pts vs 60% of placebo pts required transfusions. r-HuEPO pts required fewer units transfused (1.14 units) during Month 3 than placebo pts (2.08 units),($p \leq 0.04$) Treatment of HuEPO was associated with statistically sign. mean increase starting from baseline to last visit in both haematocrit and haemoglobin when compared to placebo for pts with low endogenous EPO levels ($p \leq 0.05$) 25% of pts in the low EPO group responded to r-HuEPO therapy vs 0 in the placebo group There was no statistically sign. differences between treatment groups in Physician's Global Evaluation or Well Being Assessment	≥20% in either group: Pyrexia Fatigue Headache Skin Reaction at medication site Nausea Cough Discontinued due to adverse exp.: N=6 Deaths: N=0

0000883

n:\reg\ab\cpmpaid\87021.cha