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 H87-037 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 to patients with AIDS who have anaemia as a result of their disease and/or concomitant AZT Therapy

Study Design: Double-blind, parallel group, placebo-controlled, randomized study in which 63 patients were enrolled and randomly assigned one of two treatment groups: Group 1 received r-HuEPO for 12 weeks and Group 2 received placebo for 12 weeks

Number of Patients: 63 patients (r-HuEPO=29 ; placebo=34)

Dosage and Admin.: 100 U/Kg, i.v., 3x/week

Duration of Treatment: 1 weeks or until haematocrit of 38-40% was reached, whichever came first

Criteria for Evaluation: The transfusion requirements (number of patients transfused per month, number of units transfused per patient per month), Well Being Assessments and Physicians' Global Evaluation were evaluated.

Summary: Benefit of r-HuEPO therapy in terms of reducing transfusion requirements and increasing haematocrit were most apparent in patients with endogenous EPO levels of $\leq$500 mU/ml. Patients with endogenous EPO levels less than or equal to 500 mU/mL were "low EPO" patients, patients with endogenous EPO levels greater than 500 mU/ml were "high EPO" patients. This categorization is based upon the reasoning that patients with high endogenous EPO levels would be unlikely to respond to supplemental r-HuEPO, whereas patients with low endogenous EPO levels would be more likely to respond to r-HuEPO therapy.

The number of low endogenous EPO, r-HuEPO-treated patients, who were transfused decreased 69% from baseline to the last month of therapy compared to a 19% decrease for placebo-treated low EPO patients. In addition, r-HuEPO therapy effectively reduced the mean number of units transfused per low EPO patient per month 36% from 1.31 at baseline to 0.84 per month during the last month of therapy vs. placebo-treated low EPO patients, whose mean number of units transfused per patient per month increased by 63% from 1.68 at baseline to 2.74 during the last month of therapy. This benefit of r-HuEPO therapy was not demonstrated in patients with high EPO levels.

Treatment with r-HuEPO was associated with a statistically significant increase in haematocrit. While the changes from baseline in well being assessment scores were not statistically significant between groups, there was a trend towards improvement for low EPO, r-HuEPO-treated patients

Safety:

Twenty-eight (97%) r-HuEPO-treated patients and 32 (94%) placebo-treated patients reported adverse experiences during double-blind therapy. The most common adverse experiences were as follows: pyrexia, fatigue, asthenia, headache, respiratory congestion and rash. All of the reported adverse events are common to AIDS patients as a group and therefore the relationship between r-HuEPO therapy and the adverse experiences is unknown.

Four patients (one r-HuEPO and three placebo) discontinued treatment because of adverse reactions during the double-blind treatment. These adverse experiences were: urticaria (r-HuEPO patient); dizziness, pain in the abdomen and extremities, paresthesia, bowel plasmacytoma and eventually death (placebo patient); rash (placebo patient); nausea, neutropenia, pain in extremities, and sinusitis (placebo patient). Two deaths were reported during the study, both occurred in patients who received placebo. The intercurrent illnesses leading to death in one patient were mycobacterium avium infection, thrombocytopenia, diarrhea and ecchymosis, the death of the second patient was due to plasmacytoma of the large bowl. There were also nine reports (four r-HuEPO, five placebo) of selected acute opportunistic infections which typically occur in patients with AIDS.

Conclusions:

The data from this study demonstrate that r-HuEPO (100 U/Kg, i.v.) can be safely administered to AZT-treated AIDS patients and is effective in significantly reducing transfusion requirements in patients with low endogenous EPO levels ($\leq$500 mU/mL).

TABLE 1

Name of Company: Ciag 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 H87-037	Double-Blind Placebo-Controlled Randomized Parallel Study	63 Group 1: r-HuEPO 29 pts 29(M) 24-52 years old Group 2: Placebo 34 pts 33(M), 1(F) 24-62 years old	AIDS Patients with Anaemia Induced by Their Disease or AZT Therapy	12 weeks or until the haematocrit rose to 38% whichever came first	Group 1: 100 U/kg r-HuEPO i.v. 3x/week Group 2: Placebo i.v. 3x/week	The effects of drug vs placebo on haematocrit and on transfusion requirements The number of patients who achieved the target haematocrit (38-40%) without transfusion within 28 days The patients Well Being Assessment and Physicians' Global Evaluation	The number pts transfused per month decreased 69% in low EPO level pts who were treated with r-HuEPO vs a 19% decrease for placebo-treated low EPO pts ($p \leq 0.05$) r-HuEPO therapy reduced the mean number of units transfused per low EPO patient per month 36% from 1.31 at baseline to 0.84 per month during the last month of therapy vs an increase in units transfused of 63% from 1.68 at baseline to 2.74 during the last month of therapy in low EPO placebo-treated pts ($p \leq 0.05$). Treatment with r-HuEPO was associated with an increase in haematocrit ($p \leq 0.05$) and haemoglobin. Results from the Well Being assessment and Physicians' Global Evaluation were similar in the two treatment groups.	≥20% in either group: Pyrexia Fatigue Asthenia Headache Respiratory Congestion Rash Discontinued due to adverse exp.: N=4 Deaths: N=2

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