| NAME OF COMPANY | PART OF THE DOSSIER | FOR NATIONAL AUTHORITY USE ONLY |
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| Cilag<br><br>Trademarks:<br>EPREX®<br><br>Name of active ingredients:<br><br>Recombinant-human Erythropoietin (r-HuEPO) | Part: IVB<br><br>Protocol H87-037<br>(Open Label)<br><br>Volume: | |

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

**Authors:** C.D.Wolleben,Ph.D.; D.J.Sullivan; E.C.Bryant,Dr.P.H.; R.I.Abels,M.D.; M.H.Christie,Ph.D.; R.Chew,Ph.D.; R.P.Danna

**Study Center:** Multicenter

**Clinical Phase:** II

**Objective:** To evaluate the safety and efficacy of long term administration of r-HuEPO in patients with AIDS who have anaemia as a result of their disease and/or concomitant therapy with AZT

**Study Design:** Double-blind, parallel group, placebo-controlled, randomized study with open-label follow-up in which 56 patients were enrolled and randomly assigned one of two treatment groups: Group 1 received r-HuEPO for 12 weeks or until hct reached 38%, whichever came first and Group 2 received placebo for 12 weeks. All patients completing the double-blind phase were eligible to enter the open-label phase of the study in which all patients were given r-HuEPO for 6 months at a dose titrated between 0 and 1500 U/Kg per week to maintain hct between 38-40%

**Number of Patients:** 56 patients (29 previously treated with r-HuEPO and 27 previously treated with placebo in H87-037)

**Dosage and Admin.:** Double-Blind: 100 U/Kg, i.v. 3x/week
Open-Label: dose titrated between 0 and 1500 U/Kg per week to maintain a haematocrit between 38-40%

**Duration of Treatment:** Double-Blind: 12 weeks or until haematocrit of 38-40% was reached
Open-Label: 6 months

**Criteria for Evaluation:** The change in transfusion requirements (number of patients transfused per month, number of units transfused per patient per month) and change in erythroid measures (haematocrit, haemoglobin, reticulocyte count) were evaluated. For patients randomized to receive r-HuEPO during double-blind therapy, the change was measured from the start of r-HuEPO during the double-blind therapy. For patients randomized to receive placebo during the double-blind therapy, the change was measured from the start of the open-label phase of the study when the patient began to receive r-HuEPO.

Summary:

Benefits of r-HuEPO Therapy in terms of improved transfusion states and increased haematocrit, haemoglobin and reticulocyte counts was most apparent in patients with endogenous EPO levels of ≤500 mU/ml

In each treatment group, patients were categorized based on their endogenous EPO level as either low EPO of high EPO. Those patients having endogenous EPO levels less than or equal to 500 mU/mL were considered "low EPO" patients whereas patients whose endogenous EPO levels were greater than 500 mU/mL were considered "high EPO" patients.

This study indicates that extended therapy with r-HuEPO was associated with reduced transfusion requirements and increased haemoglobin and haematocrit in this patient population. For low EPO patients, the monthly percent of patients transfused at baseline was 49%. During Month 3 of r-HuEPO therapy 41% of low EPO patients required transfusions, Month 6, 25% required transfusions and by Month 12 , 20% required transfusions (during this period, weekly r-HuEPO dose increased from 323 U/kg/week at Month 1 to 891 U/kg/week at Month 12). AZT dose remained between 5137 mg/wk at baseline and 3400 mg/week at month 16. The mean number of units transfused per month declined from 1.7 U at baseline to 0.8 U during Month 12. This reduction was accompanied by a statistically significant increase in haematocrit and haemoglobin.

For high EPO patients, 83% were transfused monthly during baseline period and 73% during Month 5. The percentage of patients transfused per month fell to 11% during Month 7. During Month 5, there was a reduction in the mean weekly AZT dose from 3493 mg/wk during month 4 to 2730 mg/wk during month 5 which may have allowed recovery of erythroid precursors in the bone marrow and response to ongoing r-HuEPO therapy. Unlike low EPO patients, hematologic improvement occurred in the presence of a relatively stable mean weekly r-HuEPO dose in high EPO patients after Month 5.

Fourteen patients (25%) receiving prolonged r-HuEPO therapy achieved the target haematocrit of 38% with no transfusion in the 28 days prior to the response or no more than a 40% reduction in AZT dose. In addition, sustained increases in haematocrit in low EPO patients after 12 weeks of r-HuEPO therapy, despite the progression of AIDS and continued administration of AZT, indicated that additional benefits can be obtained from extended therapy by escalating the dose of r-HuEPO in a stepwise fashion above the starting dose.

Safety:

All 56 patients in the study who were treated with r-HuEPO during this study reported at least one adverse experience. The most frequently reported adverse experiences were pyrexia, cough, diarrhea, fatigue, nausea, pneumonia, vomiting, headache, rash, respiratory congestion, GI pain, trunk pain, and insomnia.

Seven patients discontinued therapy during the open-label phase of the study. The reasons for discontinuation are as follows: progression of disease; pneumothorax; CHF, PCP; lymphoma, toxoplasmosis which eventually lead to death; weakness; PCP, pneumothorax and

bacteremia; urticaria; and MAI. Twenty-six patients who received r-HuEPO during the study died within two months of their last dose. Seven deaths were due to AIDS, nine deaths were reported as unknown cause, three were due to PCP, two from pneumonia, one from bilateral exsanguination of lungs, one from toxoplasmosis, one from respiratory failure, one from disseminated Kaposi's sarcoma, and one from MAI infection. None of these deaths were considered by the respective investigators to be related to r-HuEPO therapy.

Twenty-five (45%) of the 56 r-HuEPO-treated patients in this study experienced AIDS-defining opportunistic infections while on r-HuEPO therapy. These were probably associated with the progression of the disease (AIDS) and not thought to be treatment related.

Conclusions:

The data from this study demonstrate that long-term administration of r-HuEPO to AZT-treated AIDS patients is safe. In low EPO patients, coincident with r-HuEPO therapy, there was a reduction in transfusion requirements and sustained increase in haematocrit. This data shows that additional benefit can be obtained from extended r-HuEPO therapy by escalating the dose of r-HuEPO in a stepwise fashion above the starting dose of 100 U/Kg three-times-a-week.

High EPO patients may benefit if dose reduction of AZT occurs, but this may result in subtherapeutic levels of AZT being administered in this subpopulation. Therefore the drug should be used in high EPO patients only with close monitoring of efficacy and AZT dose.

**TABLE 1**

| Name of Company: Cilag<br>Name of Finished Product: EPREX®<br>Name of Active Ingredients: Recombinant Human Erythropoietin (r-HuEPO) | | | | Summary of Clinical Trials<br>referred to Part IV B of the dossier<br>I. PARALLEL DOUBLE BLIND STUDY WITH OPEN LABEL FOLLOW-UP | | | (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 (Open Label Follow-up) | An Open Label Follow-up to Double-Blind Placebo-Controlled Randomized Parallel Study | 56<br><br>Open Label<br><br>55(M), 1(F)<br>24-65 years old | AIDS Patients with Anaemia Induced by Their Disease or AZT Therapy | Open Label: 6 months | Open Label:<br><br>r-HuEPO titrated between 0 and 1500 U/Kg per week to maintain haematocrit between 38-40% i.v. or s.c. | The effects of r-HuEPO on haematocrit, haemoglobin, reticulocytes, and transfusion requirements | For low EPO pts, 49% were transfused at baseline: this declined to 41% during Month 3, to 25% during Month 6 and to 20% during Month 12<br><br>The mean number of units transfused per month declined from 1.7 U at baseline to 1.0 U during Month 6 to 0.8 U during Month 12. This reduction was accompanied by statistically significant increase in haematocrit and haemoglobin ($p \leq 0.05$)<br><br>For high EPO pts, 83% were transfused at baseline vs 73% during Month 5 vs 11% during Month 7<br>The haematocrit rose only after Month 5 when the mean weekly AZT dose fell below 3000 mg/week<br><br>25% of pts receiving prolonged r-HuEPO therapy achieved haematocrit of 38% . | ≥ 20% in open label:<br>Pyrexia<br>Fatigue<br>Diarrhea<br>Headache<br>Respiratory Congestion<br>Cough<br>Rash<br>Nausea<br>Pneumonia<br>Vomiting<br>GI Pain<br>Trunk Pain<br><br>Discontinued due to adverse exp.: N=7<br><br>Deaths: N=26 |

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