SANDOZ A Novartis Division

**Clinical Trial Results Website**

## Sponsor

Hexal AG

## Generic Drug Name

HX575 (Recombinant human erythropoietin)

## Trial Indication(s)

Anemia associated with chronic renal insufficiency

## Protocol Number

2007-22-INJ-17 (HX02)

## Protocol Title

Randomized, controlled, double-blind multicenter safety study to evaluate the safety and immunogenicity of subcutaneous EPO HEXAL vs. ERYPO® in the treatment of anemia associated with chronic renal insufficiency in predialysis patients

## Clinical Trial Phases

Phase III

## Study Start/End Dates

17 Oct 2007 to 11 Jan 2010

## Reason for Termination (If applicable)

The study was terminated due to the development of epoetin-neutralizing antibodies in two patients that led to the discontinuation of treatment in all other randomized patients.

## Study Design/Methodology

This study was a randomized, controlled, double-blind multicenter safety study. The individual study duration was aimed to 52 weeks of treatment (subcutaneous injection, 3x per week (t.i.w.) or weekly).

## Centers

103 centers in 10 countries: Austria (3), Bulgaria (4), Czech Republic (10), France (1), Germany (33), India (6), Poland (7), Romania (15), Russia (21), Slovakia (3)

## Objectives:

### Primary Objective:

To assess immunogenicity data of EPO HEXAL in comparison to ERYPO® after subcutaneous application in long-term treatment.

## Test Product (s), Dose(s), and Mode(s) of Administration

EPO HEXAL solution in pre-filled syringe (1000, 2000, 3000, 4000, and 5000 IU/syringe) was administered subcutaneously.

## Statistical Methods

The statistical analysis was based on the following study populations:

Safety set (SAF): all patients who received at least one dose of the study medication.

Full analysis set (FAS): all randomized patients who received at least one dose of the study medication and for whom at least one Hb value after study day 27 was available.

Per protocol set (PPS): all patients in the safety set who completed the study at least until end of study week 13 and who had no major protocol violations.

Follow-up population (FUP): All patients participating in the safety follow-up period.

The primary statistical analysis was performed for the PPS. The analysis of the primary efficacy endpoints was repeated for the FAS population as a sensitivity analysis. Two-sided 95% confidence intervals for the difference in mean change (week 13 minus baseline) in hemoglobin between EPO HEXAL and ERYPO® and the difference in the mean epoetin dose in study weeks 11-13 between EPO HEXAL and ERYPO® were computed. The difference between the treatment groups with respect to the two primary endpoints was estimated from an ANCOVA model including factors treatment, baseline Hb concentration, mean weekly dose in study weeks 11-13 (only for change in Hb levels) and country. The equivalence margins were ±1 g/dL for the change in Hb levels and ±45 IU/kg/week for the epoetin dose in study weeks 11-13. All secondary efficacy endpoints were analyzed for both the PPS and the FAS. Analysis of safety parameters was done for the SAF and the FUP. All secondary efficacy and safety variables were analyzed for each treatment group using descriptive statistics (mean, median, standard deviation [SD], minimum, maximum, quartiles) or frequency tables depending on the type (continuous / discrete) of the variable. Interim analyses were neither planned nor performed during the course of the study.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Known chronic renal insufficiency of at least 4 weeks duration; CKD stage at least 3 or higher.
- Male and female patients, age: >=18.
- Patients who are naive to ESA treatment or after 3 months of ESA-free period if previously ESA treated, (i.v. or s.c.).
- Patients with symptomatic anemia, defined as Hb level below 11.0 g/dL and not lower than or equal to 7.5 g/dL on at least 2 visits during the screening period.
- Adequate iron status, serum ferritin >= 100 µg/L or transferrin saturation >= 20%.
- Ability to follow study instructions and likely to complete all required visits and compliant with subcutaneous administration.
- Written informed consent of the patient.

Exclusion criteria

- Anemia of non-renal causes.
- Therapy with immunosuppressants (other than corticosteroids for chronic treatment) within 3 months before screening and during the study for patients with renal allograft in place or other chronic conditions (e.g. lupus erythematosus, rheumatic arthritis).

- Patients previously treated with chronic dialysis within the last 6 months (exception: one session of acute dialysis).
- Patients with acute deterioration of renal function during the screening phase according to the investigator's judgment.
- Patients receiving any RBC/whole blood transfusion during the screening period.
- Primary hematological disorder (e.g. myeloma, myelodysplastic syndrome, sickle cell anemia, hematological malignancy, hemolytic anemia).
- Evidence of uncontrolled diabetes mellitus (HbA1c > 10 % at visit -2).
- Evidence of severe hepatic dysfunction (e.g. ALT and/or AST above 2x upper limit of normal range; or gamma-GT above 3x upper limit of normal range).
- Clinical evidence of current uncontrolled or symptomatic hyperparathyroidism, defined as parathyroid hormone > 500 ng/L at visit -2.
- Uncontrolled hypertension, defined as a systolic blood pressure of >= 160 mmHg and a diastolic blood pressure measurement >= 100 mmHg (average of two values with at least one day between measurements).
- Congestive heart failure and/or angina pectoris [New York Heart Association (NYHA) class III and IV].
- History of stroke or myocardial infarction during the last 6 months prior to visit -2.
- Ongoing treatment with phenprocoumon or other cumarin derivates.
- Thrombocytopenia (platelet count <100.000/µL) or leucopenia (white blood cell count < 2.000/µL).
- Gastrointestinal bleeding within the last 6 months prior to visit -2 or hemolysis.
- Evidence of acute or chronic infection by a C-reactive protein value of > 30 mg/L.
- Suspicion or known PRCA (pure red cell aplasia).
- Previously diagnosed HIV or acute hepatitis infection.
- History of epilepsy or epileptic seizures or treatment for epilepsy within the past 6 months prior to screening.
- Planned major surgery (with expected high blood loss) during the next 3 months or major surgery within the previous 3 months (except laser photocoagulation, access surgery).
- Clinical evidence of active malignant diseases within the last 5 years (except non-melanoma skin cancer).
- Pregnancy, breastfeeding women or women not using a highly effective birth control method (e.g. implants, injectables, combined oral contraceptives, IUD, sexual abstinence, vasectomised partner).
- Known history of severe drug related allergies (e.g. anaphylactic shock).
- Known allergy to one of the ingredients of the test product or hypersensitivity to mammalian-derived products.

- Known or suspicion of any non-compliance with respect to subcutaneous treatment.
- Simultaneous participation in another clinical study or participation in a study in the month preceding visit-2 or previously randomized in this study.
- Participation in another ESA study in the 3 months preceding visit -2.
- Any other condition which at the investigator's discretion may put the patient at risk or which may confound the study results.

## Participant Flow Table

Study populations

| Description | Number of patients |
|---|---|
| Screened | 602 |
| Randomized | 337 (174 EPO HEXAL, 163 ERYPO®) |
| Safety set | 337 (174 EPO HEXAL, 163 ERYPO®) |
| Full analysis set | 328 (171 EPO HEXAL, 157 ERYPO®) |
| Per-protocol set | 267 (141 EPO HEXAL, 126 ERYPO®) |
| Follow-up population | 270 (151 EPO HEXAL, 119 ERYPO®) |

## Baseline Characteristics

Summary of demographic parameters (n=337)

| Parameter | EPO Hexal group | ERYPO® group |
|---|---|---|
| Mean age (SD) | 64.1 years (14.4) | 64.9 years (15.0) |

| | | |
|---|---|---|
| Sex | | |
| Male | 77 | 65 |
| Female | 97 | 98 |
| Mean time since CKD diagnosis (range) | 36.1 mo. (1.4-242.3) | 27.3 mo (0.9-375.1) |
| Mean Hb level at baseline (SD) | 9.7 g/dl (0.9) | 9.9 g/dl (0.9) |

## Summary of Efficacy

## Primary Outcome Result:

| Parameter | EPO Hexal group vs ERYPO® group [Per protocol set (PPS)] | |
|---|---|---|
| | Difference | 95% Confidence Interval |
| Mean absolute change in hemoglobin (baseline to end of study week 13) | -0.0117 g/dL | -0.2135 g/dL; 0.1902 g/dL |
| Weekly epoetin dose (study weeks 11-13) | 0.0195 IU/Kg | -9.9351 IU/Kg; 9.9742 IU/Kg |

## Summary of Safety

## Safety Results

A positive test for epoetin-neutralizing antibodies observed in 2 patients led to stop the study enrollment after 337 patients instead of 602, then to stop study treatment in all patients, with a 6 month safety follow-up period for all patients. In one of the 2 cases, a clinical pure red cell aplasia was associated, in the other not.

Incidence of frequent TEAEs (≥ 5% in either treatment group) during the treatment period

| | EPO Hexal group (No. of patients) | ERYPO® group (No. of patients) |
|---|---|---|
| Treatment emergent adverse events (TEAE) | 137 | 132 |

TEAEs suspected to be related to study drug

| | EPO Hexal group (No. of patients) | ERYPO® group (No. of patients) |
|---|---|---|
| TEAE (study drug related) | 28 | 25 |

**Serious Adverse Events and Deaths**

| Description | EPO Hexal group (No. of patients) | ERYPO® group (No. of patients) |
|---|---|---|
| Serious TEAE | 50 | 70 |
| Deaths | 6 | 14 |
| Discontinuation | 2 | 2 |

## Other Relevant Findings

Not Applicable

## Date of Clinical Trial Report

26 Oct 2010