SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: EPREX® (Epoetin alfa) NAME OF ACTIVE INGREDIENT(S): Recombinant human erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: EPO-OBE-01 (CR003181)

Title of Study: Effect of Early Correction Of Anaemia on the Progression of Chronic Renal Insufficiency (ECAP)

Principal Investigator: Jerome Rossert, M.D., Ph.D. - Pierre and Marie Curie University, Cordeliers Biomedical Institute and Tenon Hospital, Paris; France

Publication (Reference): none

Study Initiation/Completion Dates: 18 December 2001/14 July 2003	**Phase of development:** IV

Objectives: The primary objective was to assess the effect of an early and complete correction of anemia using epoetin alfa on the rate of progression of chronic renal failure. The primary efficacy variable was the rate of decline in glomerular filtration rate (GFR) during Phase B (the maintenance phase) to assess the progression of renal failure. Major secondary variables included severity of impairment of renal function, nutritional status, Quality of Life (QOL) and occupational status, and safety assessments.

Methodology: This open-label, two-arm, multicenter international (22 countries; 93 centers) trial randomized 390 subjects (195 in each treatment group) with chronic renal insufficiency. Subjects were randomized to 2 parallel treatment groups: high hemoglobin (Hb) target group (target Hb level: 13-14 g/dL for women, and 14-15 g/dL for men), or low Hb target group (target Hb level: 11-12 g/dL). The study comprised 3 phases: Study Entry (up to 6 months) for screening pre-randomization evaluations, Phase A (4 months) for baseline evaluations and normalization of Hb level, and Phase B (36 months) for maintenance of the target Hb level.

Number of Subjects (planned and analyzed): 630 subjects with chronic renal insufficiency were planned (315 in each of the two treatment groups). Due to early termination of the study, only 390 subjects (195 in each group) were enrolled. All 390 subjects were included in the safety analysis, and 88 (45%) and 75 (39%) of subjects in the low and high Hb target groups, respectively, were included in the primary efficacy analysis.

Diagnosis and Main Criteria for Inclusion: Male and female subjects with chronic renal failure (not associated with autosomal dominant polycystic kidney disease); between 18 and 75 years of age, inclusive; GFR between 25 and 60 mL/min/1.73m^2; rate of GFR decline below 0.6 mL/min/month; Hb level below 13 g/dL for men and 12.5 g/dL for women, without active blood loss or iron deficiency; blood pressure not above 160/100 mm Hg. Subjects were excluded for the following reasons: history of NYHA class III or IV congestive heart failure within the preceding 2 years; history of severe hypertension within the previous 3 months, history of ischemic heart disease, uncontrolled angina, coronary artery disease requiring revascularization (CABG or PTCA) or myocardial infarction within the previous 2 years; any medical condition likely to affect the response to epoetin alfa; concurrent malignancy other than non-melanoma skin carcinoma; transfusion of red blood cells within 30 days prior to study entry; administration of cytotoxic agents known to suppress erythropoiesis; concurrent chronic inflammatory condition, renal transplant; or seizure within 1 year of study entry.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (EPREX®/ERYPO®) was formulated as a sterile, colorless, preservative-free, phosphate-buffered solution containing glycine and polysorbate 80, and was provided in vials and/or prefilled syringes. Doses were administered once per week, subcutaneously (s.c.), as needed to maintain Hb in the target range, beginning with a dose of 25 to 100 IU/kg/week (for the high Hb target group) or 25 to 50 IU/kg/week (for the low Hb target group), and titrated upward as needed. Batch numbers are available on request.

Reference Therapy, Dose and Mode of Administration, Batch No.: not applicable

SYNOPSIS (CONTINUED)

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Duration of Treatment: Due to early termination of the study, subjects received epoetin alfa for an average of 6.3 and 6.8 months, in the high Hb target group and low Hb target group, respectively. Average duration of study participation was 7.9 months.

Criteria for Evaluation:

Efficacy: The primary endpoint was the rate of GFR decline from baseline (end of Phase A) to final visit. The rate of GFR decline was calculated from at least 2 GFR measurements per subject. GFR was assessed by measuring the plasma clearance of non-radioactive iohexol (Omnipaque 300®). Secondary efficacy variables included the incidence of severe renal impairment (at least 1 GFR value at or below 10 mL/min/1.73 m^2), and changes in QOL (measured with the Medical Outcomes Study Short-Form 36 questionnaire, or SF-36), occupational status (assessed using the Katz Activities of Daily Living [ADL] scale) and nutritional status (assessed by using the Subjective Global nutritional assessment, body mass index, serum albumin, serum pre-albumin, and serum cholesterol).

Safety: Safety assessments included adverse event reports, the number of hospital admissions, the number of cardiovascular events and thrombotic events, the need for renal replacement therapy, mortality and causes of death, blood pressure control, changes from baseline in vital signs, laboratory parameters and body weight, and blood management (transfusions and phlebotomies).

Statistical Methods: Analysis of the primary endpoint was based on the last observation carried forward (LOCF) approach applied to the intent-to-treat (ITT) population, which included subjects who had at least 2 GFR values during Phase B. All statistical tests were 2-sided at a significance level of 0.05. Nominal binary baseline variables were compared between both groups by Fisher's exact test, ordinal variables by Cochran-Mantel-Haenszel test, and continuous baseline variables by Mann-Whitney test. The primary outcome was the rate of GFR decline, defined as the negative of the slope of a linear regression model of GFR values against time (months). Higher positive rates indicated a faster progression of renal failure. The between-group comparison for the primary efficacy measure was performed using the Wilcoxon-Mann-Whitney test adjusting for sex.

The QOL endpoint analyses were performed using a mixed-effects model, and included all randomized subjects with at least 1 QOL score. Correlation analyses (Spearman's rank correlation statistic) were performed using the change from Month 0 to the last assessment of the three primary SF-36 domains with the rate of GFR decline (primary efficacy variable), change in GFR, and change in Hb levels, as well as the last SF-36 scores with the last GFR and Hb level. The last set of assessments in which both measures were present was used.

The occupational status was assessed using the Katz ADL scale. A two-way analysis of variance (ANOVA) model with treatment and investigator as factors was planned to be used to compare the change in the total score between the treatment groups.

For the renal impairment endpoint and nutritional status endpoint, the main comparison between groups was made for subjects in the safety population, which included all subjects who were randomized in the study. Summary statistics, including mean, standard deviation, median, and range, for all other safety endpoints were provided by treatment group

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SUMMARY – CONCLUSIONS

There were no apparent differences in demographic or baseline characteristics between the 2 treatment groups. The mean (SD) age was 58.2 (13.58) years; the majority of the randomized subjects were white (94%) and male (59%).

EFFICACY RESULTS: There was no statistically significant difference in the monthly rate of GFR decline between treatment groups (p=0.699). The monthly rate of decline was numerically lower in the high Hb target group than in the low Hb target group, indicating a slower progression of renal failure in the high Hb target group. Male subjects showed a higher rate of GFR decline than female subjects in both treatment groups (see Table below). The change in GFR values from Month 0 to the end of Phase B was also comparable across treatment groups.

Monthly Rate of GFR Decline (mL/min/1.73 m^2 per month); ITT Population

		Low Hb Target Group	High Hb Target Group
Overall	N	88	75
	Mean	0.081	0.058
	SD	1.1667	0.8978
Males	N	54	47
	Mean	0.146	0.069
	SD	1.2348	0.9508
Females	N	34	28
	Mean	-0.023	0.040
	SD	1.0591	0.8175

Because of the limited data resulting from the early termination of the study, a sensitivity analysis using a mixed-effects model was estimated to perform a GFR analysis that took into account different timing of GFR assessments among subjects using the missing at random assumption. The use of this model allowed the inclusion of all subjects with at least 1 GFR assessment during the study. Two random effects were added to incorporate individual variations in the initial GFR value and the rate of change over time. No statistically significant difference was observed in the average GFR rate during the first 9 months of Phase B. The estimated average (SE) over the first 9 months of Phase B was 18.49 mL/min/1.73 m^2 (0.778) in the high Hb target group and 18.61 mL/min/1.73 m^2 (0.703) in the low Hb target group. The model estimated a change that was negative in both treatment groups, indicating a decline over time in GFR. The comparison of the change in GFR value was not statistically significant. The decline was numerically smaller (in absolute value) in the high Hb target group (-0.260 mL/min/1.73 m^2) than in the low Hb target group (-0.465 mL/min/1.73 m^2) confirming a worse deterioration in renal function in the low Hb target group. These results confirm the primary efficacy analysis based on the rate of GFR decline measured by the negative value of the slope from a linear regression model.

The proportion of subjects with severe renal impairment (GFR at or below 10 mL/min/73 m^2 at any time) was not statistically significantly different between treatment groups, with 15% and 8% of subjects in the high and low Hb target groups, respectively, having severe impairment at some time during the study. The percentage of subjects with severe renal impairment at Month 0 was almost twice as high in the high Hb target group than the low Hb target group (10% versus 6%, respectively).

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EFFICACY RESULTS (Continued):

No statistically significant difference between treatment groups was observed in the analysis of Subjective Global nutritional Assessment (SGA; p=0.516). Almost the entire study population (96%) was well nourished both at the beginning of the stabilization phase and at the end of the study. Quality of Life SF-36 analysis suggested that a statistically significant difference between treatment groups was approached (p=0.076) in the Role Physical domain for the average score during the first 9 months of Phase B, in favor of the high Hb target group. In addition, the difference between groups at start of Phase B was statistically significant for Vitality (p=0.042), approached significance for Role Physical (p=0.055) and Physical Function (p=0.083) domains, again favoring the high Hb target group. Over the first 9 months of Phase B the estimated average SF-36 scores were numerically higher in the high Hb target group across all QOL domains except for mental health, indicating, on average, a better health status in the high Hb target group.

Positive correlations between the last QOL assessment and the corresponding Hb measure were statistically significant for 5 of the 8 domains (Role physical, Vitality, Bodily Pain Index, Social Functioning and Role emotional) of the SF-36. Correlations with GFR were statistically significant for 4 of the 8 domains of the SF-36 (Physical role functioning, Role physical, General health, and Role emotional).

For occupational status, attempts to fit a mixed effect model to the ADL scores resulted in non-convergence of the estimation procedure. This was due to the lack of variation in the ADL scores; 95% of the subjects with assessments had scores of 6 (no limitations) at the beginning of the maintenance phase and at follow-up. Only 3 subjects (2%) changed 2 or more points in either direction.

SAFETY RESULTS: Adverse events were reported by 73% of subjects in the study (72% in the low target group and 74% in the high target group). Most adverse events occurred during Phase A when Hb levels were being normalized. The most frequently reported adverse event was hypertension (12.3%), followed by upper respiratory infection (10.3%), peripheral oedema (8.7%), headache (7.4%), hyperkalaemia (6.4%), and nausea (6.2%).

Serious adverse events were reported by 15% of subjects in the low Hb target group and 17% of subjects in the high Hb target group. Myocardial infarction and peripheral ischemia were each reported by 4 subjects (1%), abdominal pain, renal failure, and hypoglycaemia were reported by 3 subjects each (0.8%), and hypertension, gastroenteritis, oesophagitis, vomiting, urinary tract infection, and hyperglycaemia were reported by 2 subjects each (0.5%).

There were slightly more hospital admissions for the high Hb target group (32; 16%) than for the low Hb target group (26; 13%). The mean duration of hospitalizations was not significantly different between groups (9.0 days in the low Hb target group and 9.7 days in the high Hb target group; p=0.678).

Cardiovascular and thrombotic adverse events were reported for 27% of subjects in the study. Those events occurred more frequently during the initial Phase A of the study. The most frequent cardiovascular/thrombotic event was hypertension (12.3% overall; 11% versus 13% for the low and high Hb target groups, respectively), followed by peripheral oedema (8.7% overall; 7% versus 11% for the low and high Hb target groups, respectively).

Eleven subjects (3%) experienced an adverse event that led to discontinuation of study drug (9 in high Hb target group and 2 in the low Hb target group). Three subjects in the low Hb target group and 1 subject in the high Hb target group withdrew due to renal replacement therapy.

There were 7 deaths (2%), 6 in the low Hb target group and 1 in the high Hb target group. All deaths were assessed as having doubtful or no relationship to study drug.

On average, blood pressure measurements over time did not change significantly in either treatment group. No clinically significant differences were observed in body weight changes over time between treatment groups. No subject received blood transfusions or phlebotomies during the study.

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CONCLUSION: Due to changes in labeling for the s.c. route of administration of epoetin alfa (EPREX ®) for the chronic renal failure indication, the Sponsor deemed it unethical to continue s.c. administration of epoetin alfa for the remainder of the study, and the study was terminated in early 2003. The strongly reduced sample size and the much shorter follow-up time than planned drastically reduced the statistical power to detect a treatment difference. In addition, the likelihood of achieving the study objectives was reduced by the limited follow-up time, given that the nature of the underlying disease requires a long observation time to detect a clinically meaningful change in renal insufficiency progression. The average study duration was 8.3 months in the low Hb target group and 7.4 months in the high Hb target group, versus the planned 3 years.

Because of the early termination of the study, the actual sample size for the GFR rate of decline analysis was 163 subjects. A posteriori power calculation revealed that 75 and 88 subjects in the high and low Hb target groups, respectively, provided only 35% power to detect a statistically significant 0.05 difference between groups in GFR rate of decline, assuming equal standard deviation of 0.2. The small sample size and the shorter time period between GFR measurements strongly reduced the statistical power to detect a treatment difference. Therefore, these results must be interpreted cautiously.

While the study was unable to demonstrate a statistically significant difference in the monthly rate of GFR decline between treatment groups, the rate of decline was numerically lower in the high Hb target group than in the low Hb target group, suggesting a slower progression of renal failure. The presence of severe renal impairment during the study was higher in the high Hb target group, but the incidence was also higher in this group at the start of Phase B of the study, and the differences between treatment groups were not statistically significant.

Quality of Life SF-36 analysis did not show a statistically significant difference in health status for the two treatment groups. However, during the first 9 months of Phase B, there was a trend toward improvement in the Role Physical domain for the high Hb group compared with the low Hb target group, and scores were numerically higher in the high Hb target group across all QOL domains except for mental health. The high Hb target group also showed either a trend toward higher mean scores or significantly higher mean scores at the start of Phase B for the domains of Vitality, Role Physical, and Physical Function.

Epoetin alfa was safe and well tolerated in this study, with no clinically meaningful differences between the two treatment groups in adverse event profiles, hospital admissions, mortality, cardiovascular or thrombotic events, or blood pressure management. The safety profile observed in this study is consistent with the well-established safety profile of epoetin alfa in this population of patients with chronic renal insufficiency.

Date of the report: 1 February 2006

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