# CLINICAL STUDY REPORT SYNOPSIS

**Document No.:** EDMS-USRA-10511952:3.0

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| Name of Sponsor/Company | Johnson & Johnson Pharmaceutical Research & Development | |
| Name of Finished Product | EPREX® (Epoetin Alfa) | |
| Name of Active Ingredient(s) | Recombinant human erythropoietin (rHu-EPO) | |

**Protocol No.:** PRI/EPO-INT-76/EPO-CA-489

**Title of Study:** A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using EPREX® (Epoetin Alfa; RWJPRI-22512) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy

**Coordinating Principal Investigator:** Brian Leyland-Jones, M.D., Department of Oncology, McGill University, [redacted], Canada

**Publication (Reference):** Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncl 2005; 23:5960-5972.

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| **Study Period:** 23 June 2000 – 5 July 2002 (double-blind phase); 1 September 2006 (follow-up phase) | **Phase of Development:** 3 |

**Objectives:** The objective of the follow-up phase was to assess long-term survival after the end of the double-blind phase.

**Methods:** This was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to evaluate the effect of maintaining hemoglobin concentration at 12 to 14 g/dL using epoetin alfa in subjects with metastatic breast cancer who were receiving first-line chemotherapy. A total of 939 subjects were enrolled in the study from 139 sites in 20 countries in Europe, Canada, South Africa, and Australia. Subjects were randomly assigned to receive either 40,000 IU epoetin alfa or placebo in a 1:1 ratio. Study drug was administered once weekly by subcutaneous injection to maintain hemoglobin concentration in the range of 12 to 14 g/dL for 12 months. Subjects who completed the 12-month double-blind phase and had the option of receiving 40,000 IU epoetin alfa once weekly to maintain hemoglobin concentration in the range of 12 to 14 g/dL in an open-label extension. Efficacy during the double-blind phase was evaluated based on the primary endpoint of overall survival and the secondary endpoints of hematologic effects, tumor response rates, time to disease progression, overall 12-month survival, RBC transfusion, and health-related patient-reported outcomes. Safety evaluations were based on the incidence and severity of adverse events, results of clinical laboratory tests, and vital sign measurements.

Based on an unblinded review of available data for 938 of the 939 randomized subjects that showed an increased mortality rate in the epoetin alfa treatment group, the Independent Data Monitoring Committee (IDMC) recommended on 24 April 2002 that study medication be discontinued for all subjects. At the time of the IDMC's review, 179 deaths (101 in the epoetin alfa treatment group, and 78 in the placebo treatment group) had been reported in the double-blind phase of the study. The IDMC further recommended that all subjects, including those who withdrew from the study, continue to have follow-up evaluations performed as described in the amended study protocol. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. agreed with the IDMC's recommendation and notified investigators and health authorities on 29 April 2002 that study medication was to be discontinued for all subjects. Subjects were to remain in the double-blind phase for its full 12-months duration. Amendment 4 to the study protocol introduced a long-term follow-up phase that required quarterly assessments for all subjects beginning 12 month after randomization, and continuing until 75% of the study population had died. That threshold was reached on 1 September 2006.

**Diagnosis and Main Criteria for Inclusion:** Eligible subjects were to have a confirmed diagnosis of metastatic breast carcinoma, including histology of the primary tumor. Subjects were female, at least 18 years of age, were starting first-line chemotherapy, had an ECOG Performance Status score of 0, 1, or 2, and had a life expectancy of at least 6 months. Subjects were excluded if they had brain metastases or leptomeningeal disease, if they were receiving dose intensification chemotherapy for bone marrow or stem cell transplantation, if they had an active second primary malignancy, or if there were causes of anemia known to be unresponsive to epoetin alfa.

Before Amendment 4 of the protocol, subjects who completed the double-blind phase were eligible to participate in the open-label phase. All other subjects entered long-term follow-up. Amendment 4 implemented long-term

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follow-up for all subjects.

**Test Product, Dose and Mode of Administration, Batch No.:** Epoetin alfa (EPREX®) was formulated as a sterile, colorless, preservative-free, phosphate-buffered solution, and was supplied in single-use vials. Study drug was administered during the open-label phase at an initial dose of 40,000 IU once weekly. Dosage adjustments during the open-label phase were based on monitored hemoglobin concentrations and rate of hemoglobin increase. The maximum dose of study drug was not to exceed 60,000 IU/week. Bulk lot numbers used during the study were D00PD7106, D00PH7020, D00PK7024, D01PD7060, and D02PA7135.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** N/A during the open-label phase.

**Duration of Treatment:** The duration of the double-blind phase was 12 months. The follow-up phase was to be continued until 75% of the study population had died.

**Criteria for Evaluation:**

Efficacy: Before protocol amendment 4, the following efficacy evaluations were to be performed every 6 months for subjects participating in the open-label phase: survival status and RBC transfusion information, measurement of hematologic effects (hemoglobin concentrations and reticulocyte counts), assessment of malignancy status, and collection of information regarding chemotherapy, hormonal therapy, and radiotherapy. For subjects who had withdrawn from the double-blind phase, who had completed the double-blind phase but were not participating in the open-label phase, or who stopped participation in the open-label phase, the following information was to be collected every 6 months: survival status, use of commercial erythropoietin, and information regarding therapy that could affect survival status (e.g., chemotherapy and hormonal therapy) Following Amendment 4, quarterly evaluations collected survival status, last available hemoglobin concentration, ECOG Performance Status score, and details regarding commercial ESA, chemotherapy, and hormonal therapy for all subjects.

Safety: Before protocol amendment 4, subjects participating in the open-label phase were evaluated every 6 months for the collection of vital signs, adverse event, and serious adverse event information, and for hematology and iron measurements. Following Amendment 4, quarterly evaluations were limited to the collection of serious adverse event information for all subjects in follow-up.

**Statistical Methods:** All efficacy analyses of post-double-blind phase data were to be descriptive in nature. The Kaplan-Meier estimate of long-term survival was to be presented by treatment group for the intent-to-treat population. The stratified (by metastatic category) log-rank test was to be used for treatment comparison.

Two methods of data censoring were to be used for the analysis of long-term survival. The first method censored all subjects who were lost to follow-up at the last date they were known to be alive. The second method censored subjects who were treated with placebo during the double-bind phase at the start date of ESA treatment (either open-label epoetin alfa or any commercial ESA product) after the double-blind phase. In this alternative censoring method, subjects originally assigned to the epoetin-alfa treatment group, and subjects originally assigned to the placebo treatment group but who did not receive an ESA after the double-blind phase, were censored at the latest date known to be alive. Cox's proportional hazard model stratified by metastatic category was to be used for calculation of a hazard ratio and its associated 95% confidence interval.

Descriptive statistics (mean, standard deviation, median and range) for hemoglobin concentrations at 4-week intervals was to be presented for the treated open-label population.

A listing of adverse events, serious adverse events, and thrombotic vascular events for the treated open-label population were to be provided and summarized by body system, preferred term, included term, severity, and relationship to study drug. A listing of serious adverse events for the safety follow-up population was to be provided and summarized by original double-blind treatment group assignment.

**SUMMARY - CONCLUSIONS**

EFFICACY RESULTS: Of the 715 subjects who had died as of the clinical cutoff date, 362 of 470 (77%) subjects were originally assigned to the placebo treatment during the double-blind phase; 353 of 469 (75%) subjects were originally assigned to the epoetin alfa treatment group. Median overall survival was 22 months and 21 months for subjects originally assigned to the placebo and epoetin alfa treatment groups, respectively. The p value for the overall survival comparison between the 2 treatment groups was 0.602 (Cox proportional hazards model and log-rank test). The hazard ratio for epoetin alfa treatment versus placebo treatment was 1.04 (95% CI: 0.90 to 1.20).

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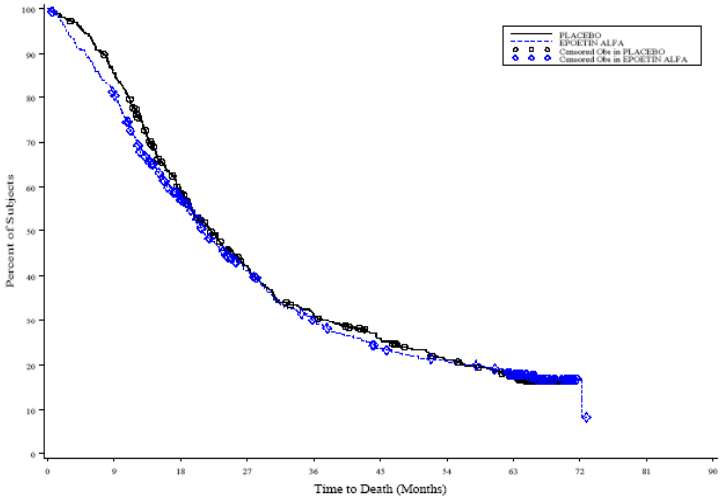
Kaplan-Meier Curve of Overall Survival: All Subjects Censored at the Last Date Known to be Alive
(Study EPO-INT-76: Intent-to-Treat Population)

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This finding was supported by a sensitivity analysis of overall survival in which subjects assigned to the placebo treatment group during the double-blind phase were censored at the time they received open-label epoetin alfa or another ESA.

The median hemoglobin concentration at the start of the open-label phase (before the first dose of open-label epoetin alfa) was 11.9 g/dL for subjects who had been assigned to the placebo treatment group during the double-blind phase and 12.4 g/dL for subjects formerly assigned to the epoetin alfa treatment group. The median hemoglobin concentration at end point (last measurement recorded during the open-label phase) was 12.8 g/dL for subjects formerly assigned to placebo treatment as well as for subjects formerly assigned to epoetin alfa treatment during the double-blind phase.

SAFETY RESULTS: Of the 228 subjects who received at least 1 dose of open-label study drug, 63 (27.6%) experienced an adverse event and 25 (11.0%) experienced a serious adverse event following the double-blind phase. With the exception of "condition aggravated", which was reported for 5 subjects, no serious adverse event was specified more than twice. Disease progression was the most frequently cited cause of death, with 340 (72.3%) subjects originally assigned with the placebo treatment and 326 (69.5%) subjects originally assigned to the epoetin alfa treatment group having disease progression specified by the investigator as the cause of death. This was consistent with the investigator-cited causes of death reported for the double-blind phase. Seven (1.5%) subjects from each of the double-blind treatment groups had fatal thrombotic vascular events specified as the cause of death during the study or follow-up period.

CONCLUSION: The conclusions drawn from the double-blind phase, i.e., that maintenance of hemoglobin concentration in the range of 12 to 14 g/dL with epoetin alfa at a weekly dose of 40,000 IU in women with metastatic breast cancer who were receiving chemotherapy is associated with significantly increased 12-month mortality, remains unchanged following the analysis of long-term follow-up data. However, Kaplan-Meier estimates of survival beyond the double-blind end point of 12 months suggest that epoetin alfa treatment did not affect long-term survival, as evidenced by the convergence of the survival curves for the placebo and epoetin-alfa treatment groups 15 to 18 months after the start of double-blind treatment. Similarly, treatment with epoetin alfa during the double-blind phase did not appear to have a clinically meaningful effect on the types or incidence of adverse events or serious adverse events experienced by subjects during long-term follow-up.

**Issue Date of the Clinical Study Report:** 26 September 2007