SYNOPSIS

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

Protocol No.: EPO-IMU-401 and EPO-IMU-402

Title of Study: An Active Safety Surveillance Plan to Prospectively Monitor the Incidence of Pure Red Cell Aplasia (PRCA) Among Patients Receiving Epoetin Alfa Therapy or Other Erythropoietins and An Active Safety Surveillance Plan to Conduct Serologic Testing for Anti-Erythropoietin Antibodies and Prospectively Monitor the Incidence of Pure Red Cell Aplasia (PRCA) Among Patients Receiving Epoetin Alfa or Another Erythropoietin

Coordinating Investigator: Jerome Rossert, M.D., Ph.D. – Service de Nephrologie, Hôpital Tenon, Paris; France

Publication (Reference): None

Study Initiation/Completion Dates: 20 January 2003 to 31 July 2005. **Phase of Development:** IV

Objectives: The primary objectives were to: 1) prospectively monitor the incidence of pure red cell aplasia (PRCA) among subjects with chronic renal failure (CRF) who were receiving treatment with epoetin alfa or other exogenous recombinant erythropoietin therapies, 2) estimate the prevalence and development of erythropoietin (EPO) antibodies associated with different routes of administration and formulations, and 3) examine the natural history of EPO antibodies and its relationship to PRCA.

The secondary objectives of both Studies EPO-IMU-401 and EPO-IMU-402 were to: 1) estimate the incidence rate of PRCA associated with different routes of administration for epoetin alfa or other recombinant erythropoietins in the treatment of CRF, 2) actively monitor a change in the incidence of PRCA over time among subjects receiving epoetin alfa or other recombinant erythropoietins for CRF as may occur with changes in usage patterns or manufacturing, 3) collect sufficient prospective data from PRCA cases and non-PRCA cases to assist with the later identification of risk factors for PRCA such as demographic profile and duration of exposure to epoetin alfa or other recombinant erythropoietins, 4) provide a framework for the expansion of the subject population to estimate the incidence of PRCA associated with the use of epoetin alfa or other recombinant erythropoietins for other therapeutic indications, and 5) collect all available information on lot numbers of recombinant erythropoietin products administered to the subjects.

An additional objective of Study EPO-IMU-402 was to actively monitor a change in the occurrence of EPO antibodies over time among subjects receiving epoetin alfa or other recombinant erythropoietins for CRF as may occur with changes in usage patterns or manufacturing.

Study Methods: Studies EPO-IMU-401 and EPO-IMU-402 were observational cohort studies to prospectively monitor the incidence of PRCA among subjects with CRF who were receiving treatment with epoetin alfa or other recombinant erythropoietin therapies. There was no experimental component (treatment or procedures) or change in health care practice associated with these surveillance plans, except for the periodic collection of blood for serologic testing in Study EPO-IMU-402. No laboratory tests were required for the conduct of Study EPO-IMU-401. Study EPO-IMU-402 used methods of diagnosis of PRCA observation identical to those of the Study EPO-IMU-401, and contributed to the target numbers and data for a combined analysis.

Following subject informed consent, the following variable information was collected at enrollment: age, sex, race, dialysis status, indication for treatment with recombinant erythropoietin (e.g., etiology of renal disease), previous recombinant erythropoietin use (including start date, formulation and route of administration), recombinant erythropoietin formulation given, route, dose and frequency of administration.

Approximately every 3 months following enrollment, sites were asked to collect and document subject progress information. This information included whether or not the subject was still using a recombinant erythropoietin therapy (and if not, why not), current recombinant erythropoietin formulation used, route, dose, frequency, reticulocyte count and the presence of any signs of PRCA development. If a confirmed or suspected diagnosis of PRCA was made, the date of diagnosis was collected. In addition to collecting information on PRCA cases, the presence of any case criteria of PRCA development was evaluated as an adverse event (AE).

SYNOPSIS (CONTINUED)

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Study Methods: (continued) As part of Study EPO-IMU-402, serum samples were collected at baseline and 3 months for the purpose of screening/monitoring for EPO antibodies. If, during the course of the study, the investigator suspected PRCA or lack of effect (LOE), an additional serum sample for antibody testing was drawn. Subjects with positive EPO antibody tests were offered an immediate sera collection for confirmation and then monthly sera collection for testing until the subject became negative, at which time the previous schedule of every 3 months was resumed.

Number of Subjects (planned and analyzed): The planned sample size was a total of 20,000 patients in the 2 studies combined. There were 10,078 patients enrolled in studies EPO-IMU-401 and EPO-IMU-402. A total of 9,791 subjects (4,636 in EPO-IMU-401 and 5,242 in EPO-IMU-402) were analyzed, with 287 subjects excluded from analysis due to protocol violation.

Enrollment in Studies EPO-IMU-401 and EPO IMU-402 was stopped in July 2004, when it became apparent that the study objectives could not be achieved due to the contraindication of s.c. administration of the polysorbate 80-containing EPREX formulation in Europe (and restrictions on the route of administration used in other countries [e.g., Australia and Canada]) and recognition that the risk of PRCA occurs predominantly with s.c. administration of EPREX in renal patients. This action was taken because a sufficient number of patients exposed to s.c. EPREX could not be enrolled to make valid conclusions about the incidence rate of PRCA in a patient population treated with s.c. recombinant erythropoietins.

Diagnosis and Main Criteria for Inclusion: The population consisted of patients receiving or about to receive treatment with a recombinant erythropoietin as part of a pre-existing management plan for their chronic renal failure.

Test Product, Dose and Mode of Administration, Batch No.: Not Applicable

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable

Duration of Treatment: Not Applicable

Statistical Methods: The prospective cohort studies conducted are observational in nature and do not mandate any treatment intervention. The studies were conducted to observe the outcomes of treatment initiated through standard medical management (i.e., not as a result of randomization or other form of patient assignment). Due to the observational nature of the studies, all analyses performed are descriptive in nature. No statistical analyses were performed for the purpose of this report.

SUMMARY – CONCLUSIONS

SAFETY RESULTS: There were 10,078 patients enrolled in studies EPO-IMU-401 and EPO-IMU-402. A total of 9,791 subjects across both studies were analyzed: 4,636 and 5,242 subjects, in studies EPO-IMU-401 and EPO-IMU-402, respectively (87 of these subjects were enrolled at both sites). At registration, 6,456 (66%) subjects were scheduled to receive i.v. recombinant erythropoietins, and 3,330 (34%) subjects were scheduled to receive s.c. recombinant erythropoietins. The most commonly scheduled s.c. erythropoietin at registration was EPREX (N=1,570), followed by Aranesp (N=1,222) and NeoRecormon (N=535). For those subjects receiving Aranesp and NeoRecormon, brand and route of administration remained consistent from the time of subject registration to last assessment. However, the numbers of subjects receiving i.v. and s.c. EPREX decreased substantially from registration to last assessment. The number of subjects receiving i.v. EPREX decreased from 4,909 subjects at registration to 3,393 subjects at last assessment, and the number of subjects receiving s.c. EPREX decreased from 1,570 subjects at registration to 678 subjects at last assessment.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (continued)

SAFETY RESULTS: (continued) The results of studies EPO-IMU-401 and EPO-IMU-401 show that there were no cases of PRCA reported among the 9,791 subjects. There were only 15 subjects who reported LOE, all of whom tested negative for EPO antibodies. The prevalence of EPO antibodies was shown to be very low in a CRF patient population. Of the 5,035 subjects providing at least one antibody test sample, only 1 subject had positive EPO antibody results. This subject did not develop PRCA.

CONCLUSION: During the conduct of studies EPO-IMU-401 and EPO-IMU-402, it was recognized from spontaneous reports that the s.c. route of administration was associated with all of the risk of PRCA related to EPREX exposure, and that most of this risk was due to one product formulation of EPREX that was recalled. These studies were not designed to selectively enroll and follow subjects with only s.c. exposure. Although close to 10,000 subjects were enrolled, only 1,677 person-years of s.c. EPREX exposure were observed. Consequently, these studies were underpowered to specifically examine the risk of PRCA (at the level of fewer than 10 cases per 100,000 person-years in spontaneous reports) with s.c. exposure to the EPREX formulations that continued to be marketed.

There was only 1 isolated case of borderline positive EPO antibodies in studies EPO-IMU-401 and EPO-IMU-402. Across these studies, there were 15 cases of LOE identified but no cases of PRCA. It is not uncommon to see some resistance to recombinant erythropoietin treatment, as LOE has several potential causes other than PRCA, including the following: absolute and relative iron deficiency, infection and inflammation, hyperparathyroidism, aluminum overload, hemoglobinopathies (e.g., sickle cell disease or thalassemia), multiple myeloma or other malignancies, cofactor (vitamin B_{12}) deficiency, hemolysis, malnutrition, chronic blood loss, inadequate dialysis, or adverse effects related to immunosuppressive agents and angiotensin converting enzyme inhibitors.

Studies EPO-IMU-401 and EPO-IMU-402 provided the Company with valuable experience in conducting large-scale observational studies among patients with CRF with the objective of monitoring for a very rare event. It also showed that, while enrollment in these kinds of prospective surveillance studies with large-scale antibody testing was possible, it was extremely difficult to find justification for such antibody screening in the absence of clinical symptoms of PRCA or to obtain sufficient data to generate meaningful conclusions on the clinical value of such antibody tests among asymptomatic patients.

Date of the report: 02 June 2006

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