SYNOPSIS

Issue Date: 25 January 2012

Name of Sponsor/Company	Janssen Research & Development
Name of Finished Product	EPREX®
Name of Active Ingredient(s)	epoetin alfa

Protocol No.: EPO-ANE-4014

Title of Study: A Prospective, Immunogenicity Surveillance Registry (PRIMS) to Estimate the Incidence of Erythropoietin Antibody-Mediated Pure Red Cell Aplasia Among Subjects With Chronic Renal Failure and Subcutaneous Exposure to Recombinant Erythropoietin Products

ClinicalTrials.gov Identifier: NCT00391287

Clinical Registry No.: CR011587

Registry Center(s): The registry was conducted in 15 European Union (EU) countries, Norway, Switzerland, and Australia.

Publication (Reference): None

Study Period: 30 June 2006 to 31 December 2010. Database lock date: 06 July 2011.

Phase of Development: 4

Objectives: The primary objective for the PRIMS registry of subjects with chronic renal failure (CRF) was to estimate the incidence rate of erythropoietin (EPO) antibody (Ab)-mediated pure red cell aplasia (PRCA) with subcutaneous (SC) exposure to the polysorbate 80 formulation of EPREX® and to compare this incidence rate to the incidence rate with SC exposure to other currently marketed recombinant erythropoietin products (epoetin alfa, epoetin beta, darbepoetin alfa) with adjustment for duration of exposure.

The secondary objective was to examine, in sensitivity analyses of the incidence rates of EPO Ab-mediated PRCA and their rate ratios, the impact of the patterns of mixed SC exposure to multiple erythropoietin products occurring in this subject population and of varying the assumption of 1 to 12 months for latency from exposure to the onset of PRCA.

Methodology: This was a multicenter, multinational, non-interventional, immunogenicity surveillance registry. The registry employed a prospective, observational, cohort design with enrollment of parallel groups that were exposed to the polysorbate 80 formulation of EPREX and other marketed erythropoiesis-stimulating agents (ESAs) administered SC for treatment of the anemia of CRF and used according to standard practice consistent with the terms of the marketing authorization. Informed consent was obtained according to local regulations to safeguard the privacy of subjects and to ensure cooperation for investigation and follow up of potential cases of PRCA.

Subjects were to be observed for the development of PRCA for up to 3 years. Information on exposure to ESAs, stage of CRF, treatment modality for CRF, ESA handling and storage information, and most recent hemoglobin value was collected quarterly from the subjects' medical notes and transferred to the registry case report form. Cases of unexplained loss of effect (LOE) with an administered ESA, including cases of suspected PRCA, were reported to the Sponsor as serious adverse events (SAEs). EPO antibody testing

was recommended for cases of suspected PRCA. Healthcare providers were encouraged to use the laboratory validated by the Sponsor.

Final PRCA case confirmations, including date of LOE onset, number of ESA brands used by the subject, and relationship with specific ESA(s), were adjudicated by an Independent Case Adjudication Committee (ICAC) which reviewed treatment-blinded ESA case data for subjects with unexplained LOE with positive or borderline antibody testing.

Number of Subjects (planned and analyzed): As planned in the protocol, the Sponsor was to actively monitor registry enrollment and ESA brand usage to ensure that the registry accrued 20,000 person-years (PY) of SC exposure to EPREX and 20,000 PY of SC exposure to all other ESAs combined. In investigational sites in which 1 registry arm met this accrual goal before the other, the Sponsor elected to selectively close those sites with predominant use of the ESA(s) in the arm approaching full accrual.

Enrollment in the registry ended prior to achievement of this target accrual (See Registry Limitations), as agreed upon with the Agence française de sécurité sanitaire des produits de santé (Afssaps).

Diagnosis and Main Criteria for Inclusion: Registry subjects included adult men and women with CRF who were receiving or were about to receive (within 1 month of the date of enrollment) a marketed ESA by the SC route of administration and were likely to continue receiving the product for at least 1 year. Potential subjects must have provided informed consent as required by local regulations.

Test Product, Reference Therapy, Dose and Mode of Administration, Batch No.: The therapy of interest was EPREX by SC route of administration. Reference therapies included the recombinant ESAs Aranesp® (darbepoetin alfa) and NeoRecormon® (epoetin beta). The Sponsor did not supply any ESAs or other medications.

Criteria for Evaluation: Cases of EPO Ab-mediated PRCA were to be determined by the clinical presence of an unexplained LOE with administered ESA, suspected PRCA, and the presence of EPO antibody. Healthcare providers at participating sites were instructed to report cases of unexplained LOE, including cases of suspected PRCA, that occurred within the enrolled cohort. Healthcare providers were also instructed to report all other SAEs suspected of being causally related to the use of any ESA with additional reporting done as required by local regulations in certain jurisdictions. Any additional adverse events (AEs) reported to the Sponsor were processed by standard operating procedures and local regulations.

Final PRCA case confirmations, including date of LOE onset, number of ESA brands used by the subject, and relationship with specific ESA(s), were adjudicated by an ICAC.

Statistical Methods: Incidence rates were estimated as the total number of cases of EPO Ab-mediated PRCA attributed to a specific product divided by the PY of SC exposure (defined as the time during the registry when a subject was exposed to a specific treatment) or observed time (defined as the time the subject was at risk for PRCA) for that product over all stages and treatment modalities of CRF (e.g., predialysis, peritoneal dialysis, hemodialysis). Incidence rates were adjusted for duration of exposure by stratification. Sensitivity analyses with varying assumptions on the latency from exposure to erythropoietin product to onset of PRCA were employed to address the possible effect on the estimates of switches in therapy, exposure to multiple erythropoietin products by the SC route of administration, discontinuation of therapy, and withdrawal from observation. Confidence intervals for rate estimates were calculated using the Poisson distribution for rare events.

RESULTS:

REGISTRY POPULATION: The PRIMS registry enrolled a total of 15,333 subjects; 9,602 (62.6%) subjects completed the registry. At the initial study visit, 5,948 subjects were receiving EPREX, 5,974 subjects were receiving Aranesp, and 3,382 subjects were receiving NeoRecormon. Twenty-nine subjects did not have treatment data available due to minor protocol violations (i.e., ESA treatment started more than 1 month after baseline visit). A total of 5,731 (37.4%) subjects did not complete the registry. The most commonly recorded reasons for discontinuation across all treatments were death (17.1%) and lost to follow up (16.6%). Other reported reasons (≥1%) for treatment discontinuation included AEs (2.1%) and administrative (1.1%).

The study population consisted of primarily predialysis (80.5%), male (56.5%), and white (96.6%) subjects. The median age was 73 years. Subject demographics were comparable across all treatments with some exceptions. The mean age of subjects receiving EPREX was 71.1 years, as compared with 69.1 years for those receiving Aranesp and 69.5 years for those receiving NeoRecormon. More subjects receiving NeoRecormon were on dialysis (27.9%) compared with those receiving EPREX (17.6%) or Aranesp (16.7%). Dialysis patients on EPREX were more likely to have received hemodialysis (83.3%), rather than peritoneal dialysis, as compared with dialysis patients on Aranesp (61.3%) and NeoRecormon (78.2%). The causes of CKD were generally similar across treatment groups and were as expected for a population with CKD.

Subjects receiving EPREX entered the registry at a lower hemoglobin value (10.9 g/dL) than subjects receiving Aranesp (11.4 g/dL) or NeoRecormon (11.2 g/dL). Overall, EPO naïve subjects entered the registry at a lower hemoglobin value (10.1 g/dL) than non EPO naïve subjects (11.2 g/dL). More subjects receiving EPREX were EPO naïve at the time of enrollment (2,536 subjects; 49.7%) than subjects receiving Aranesp/NeoRecormon (2,130 subjects; 24.3%).

Subjects were considered to have received ESA treatment continuously if no more than 30 days had elapsed between doses of the same ESA and no other ESA product was given between those doses. Exposure time was calculated for each SC treatment of EPREX, Aranesp, or NeoRecormon using a review of the previous 12 months exposure to determine single exposure versus mixed. Subjects' exposure was terminated at the first administration of any non-study ESA. As of 31 December 2010, a total of 15,333 subjects had been enrolled in the registry. For these subjects with exposure data, there were 8,377 PY of exposure to EPREX and 14,286 PY of exposure to other ESAs. Overall, 6,525 subjects had EPREX exposure with a mean exposure of 15.4 months; 6,565 subjects had Aranesp exposure with a mean exposure of 17.0 months; 3,811 subjects had NeoRecormon exposure with a mean exposure of 15.7 months; and 9,925 subjects had either Aranesp or NeoRecorman exposure with a mean exposure of 17.3 months.

PRCA RESULTS: The incidence of PRCA was evaluated in terms of exposed time (defined as the time during the registry when a subject was exposed to a specific treatment) and, separately, in terms of observed time (defined as the time the subject was at risk for PRCA). There were 3 cases of EPO Ab-mediated PRCA with EPREX and 2 cases with other ESAs (1 case with Aranesp and 1 case with NeoRecormon) reported during the conduct of the registry. When comparing the incidence rates based on exposed time, the rate for the 3 EPREX cases was 35.8/100,000 PY, the rate for the 2 Aranesp/NeoRecormon cases combined was 14.0/100,000 PY, and the rate ratio was 2.6 (95% CI: 0.43, 15.31). Based on observed time, the incidence rates were: EPREX 37.6/100,000 PY, Aranesp/NeoRecormon 13.9/100,000 PY, rate ratio: 2.7 (95% CI: 0.45, 16.15). These rates and rate ratios are similar to those based on exposed time seen in the interim report (EPREX 37/100,000 PY, Aranesp/NeoRecormon 15/100,000 PY, rate ratio: 2.5 [95% CI: 0.29, 29.9]). The 90% and 95% CIs for the incidence rates overlapped. Confidence intervals for the rate ratios overlapped unity. The incidence

rate differences for both exposed and observed time rate ratios were not statistically significant (p value greater than 0.05).

SAFETY RESULTS: Of 15,333 subjects enrolled in the registry, drug-related SAEs were reported in 25 subjects. The most commonly reported events were blood and lymphatic system disorders (8 subjects), including PRCA, suspected PRCA, unexpected anemia, and erythroblastopenia and general disorders and administration site conditions (5 subjects), including LOE, possible LOE to EPO, decreased therapeutic response, and EPO loss of effect. A review of AEs and SAEs did not reveal any new or unexpected safety concerns.

Of 2,936 subjects who died during the conduct of the registry, 1 death was assessed to have a contributory factor (bronchial cancer; not pathologically confirmed) felt by the investigator to be possibly related to EPREX, 2,809 deaths were assessed to have no or doubtful relation to ESA treatment, and 126 deaths were assessed as having had an unknown relationship to ESA treatment.

While EPO naïve subjects entered the registry at a lower hemoglobin value than non EPO naïve subjects, hemoglobin values were similar between the 2 groups after 3 months and remained similar throughout the conduct of the registry. Although subjects receiving EPREX entered the registry at a lower hemoglobin value than subjects receiving Aranesp or NeoRecormon, the hemoglobin values were similar between the treatment groups after 3 months and remained similar throughout the conduct of the registry. No substantial variations in hemoglobin values over time were noted.

REGISTRY LIMITATIONS: Apart from the limitations inherent in observational studies (non-interventional, non-randomized and non-placebo controlled study design), and the fact that only a small number of PRCA cases were reported, no other notable limitations were identified by the Sponsor. Changes in the ESA environment, including decreasing recruitment rates, the impact of ESA switching on the number of evaluable registry subjects, class labeling restrictions on the use of ESAs in renal populations, and the introduction of ESA biosimilars, impacted enrollment and the ability of the registry to fulfill the objectives outlined in the registry protocol.

CONCLUSIONS: The registry was terminated prematurely due to accrual being less than anticipated. In this large, multinational, non-interventional, surveillance registry, EPO antibody mediated PRCA occurred at a very low incidence with the therapeutic use of EPREX and other ESAs. Although the rate observed among PRIMS subjects exposed to EPREX was higher than the rate observed among subjects exposed to comparator ESA treatments, this difference was not statistically significant. The findings from this registry support that SC polysorbate 80 EPREX formulations with coated stoppers have a similar and acceptable immunogenic safety profile relative to NeoRecormon and Aranesp. Since biosimilar ESAs were excluded from this registry, comparison of the EPREX, NeoRecormon, and Aranesp immunogenicity risk to biosimilars is not possible.

No new, unexpected, or unusual safety signals were noted during the conduct of the registry. The Sponsor will continue to review all spontaneously reported LOE cases using the enhanced EPREX RMP EPP to monitor and report world wide EPREX PRCA reporting rates.