SYNOPSIS

Issue Date: 14 June 2011

Name of Sponsor/Company	Janssen-Cilag BV, the Netherlands
Name of Finished Product	Eprex
Name of Active Ingredient(s)	epoetin alfa

Protocol No.: EPOCAN4018

Title of Study: Survey on the Treatment of Anemia using Recombinant human erythropoietin 2

Study Name: STAR-2

Coordinating Investigator: Not applicable (none appointed)

Publications (Reference):
- Van den Bosch J, Kerkhofs LGM, Braun JJ, et al. Anaemia management with epoetin alfa in real-life, daily oncology practice in the Netherlands. Interim analysis results from an observational study. Poster presented at ECCO, September 2007

- Van den Bosch J, Kerkhofs LGM, Braun JJ, et al. Anaemia management with epoetin alfa in daily oncology practice. Interim analysis results from a Dutch observational study.
Poster presented at ESMO, September 2008

- Lunde R, Strankinga WFM, Van den Berg PM, et al. Anaemia management with epoetin alfa in patients with lung cancer. Interim analysis results on lung cancer patients of a Dutch observational study. Poster presented at WCLC, August 2009

- Kehrer DFS, Van den Bosch J, Braun JJ, et al. Anaemia management with epoetin alfa in patients with cancer. Interim analysis results of a Dutch observational study. Poster presented at ECCO 15 / ESMO 34 conference, Berlin, Germany, 20 – 24 September 2009. European Journal of Cancer Supplements, Vol 7 No 2, September 2009, Page 183 (abstract P-3026).

- De Boer, J. van den Bosch, L.G.M. Kerkhofs, F.A.A. Valster, N.J.J. Schlösser, R. Lunde, J.G.J.V. Aerts, R.G.P.M. Brok, M. Lahaye, M.D. Franken. Dutch observational study on anaemia management with epoetin alfa (Eprex®). Abstract published at ASCO, June 2011

- N.J.J. Schlösser, R. Lunde, J.G.J.V. Aerts, M. Heijsteeg, W.F.M, Strankinga, R.G.P.M. Brok, M. Lahaye, M.D. Franken. Dutch observational study on chemotherapy-induced anaemia management with epoetin alfa (Eprex®) – Sub-analysis on lung cancer patients. Poster presentation at WCLC, July 2011

Study Period: 3 November 2005 - 5 November 2009

Phase of Development: Phase 4

Objectives: To investigate the safety and efficacy of epoetin alfa for treatment of anemia in cancer patients, with special attention for: 1. Practice: at which Hb level is treatment started, what dosing schedule(s) and dosing adaptations are used, duration of treatment and current practice in of iron supplementation; 2. Efficacy: % responders, mean Hb response; 3. Adverse events.

Methods: Prospective, observational, multi-center, single-country, open-label study in cancer patients treated for anemia with Eprex (epoetin alfa).

Number of Patients (planned and analyzed): Planned: 1928; analyzed: 1927.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

1. 18 years or older;
2. having solid tumors, multiple myeloma (Kahlers' disease), non-Hodgkin lymphoma or Hodgkins' disease;
3. already receiving chemotherapy or starting their first cycle within a week;
4. receiving epoetin alfa treatment, with an expected treatment duration of at least 4 weeks according to local label;
5. having signed written informed consent, for use of their coded data.

Exclusion criteria

1. patients who cannot read the Dutch language and/or do not understand the Dutch Informed Consent form
2. patients who participated in other studies with epoetin alfa in cancer patients (EVALUATE, COMPARE).

Test Product, Dose and Mode of Administration, Batch No.: Commercially available Eprex (epoetin alfa).

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

Duration of Treatment: Patients were followed during their epoetin alfa treatment and data were recorded on average once a month (depending on the treatment modality) from the start of epoetin treatment until 4 weeks after the end of epoetin alfa treatment.

Criteria for Evaluation:

1. Primary efficacy variable: Number and percentage of responders, where defined as patients with an Hb increase of at least 1 g/dl during the first four weeks of epoetin treatment or, if they do not fulfill this criterion, patients that maintained Hb ≥12 g/dl from 5 weeks after the start on epoetin alfa treatment, with and without interference of transfusions within the preceding 28 days.

2. Secondary efficacy variables:

   (1) number of responders based on the alternative definition, i.e. patients with an Hb increase of at least 1 g/dl during the first four weeks of epoetin treatment or, if they do not fulfill this criterion, patients with a Hb increase of at least 2 g/dl after start of epoetin treatment or, if they do not fulfill this criterion, patients that maintain a Hb between 11 and 13 g/dl from 4 weeks after the start on epoetin alfa treatment, either with or without transfusion within the preceding 28 days;

   (2) hemoglobin levels over time;

   (3) number and percentage of patients with transfusions including transfusion volumes;

   (4) epoetin alfa treatment schedule (Hb level at treatment initiation, dosage and treatment duration);

   (5) time to response;

   (6) iron supplementation.

3. Safety evaluation: (Treatment-emergent) (serious) adverse events, Deaths, Thrombotic adverse events, all with their possible relation to study medication, action taken and outcome.

In addition, data were analyzed for the total study populations as well as the following subgroups: 70 years or older (≥70); patients with breast and gynecological cancer (BGC); patients with lung cancer (LC); patients with NSCLC; patients with SCLC.

Statistical Methods:

- Description of nominal parameters with absolute numbers, percentages and frequency distributions;
- Description of continuous and ordinal parameters with mean, standard deviation, median, range and 95% confidence interval;
- Kaplan-Meier estimates for time to Hb response curves.
- Shifts in Hb values were tested using the Wilcoxon signed rank test, interpreted at the 5% significance level (2-tailed), and associated p-values are presented.

No statistical testing was performed to compare results of the total study population and the subgroups.

RESULTS:

1927 patients were included and analyzed; the efficacy analysis included 1744 patients. The analyzed subgroups comprised 605 patients aged ≥70 years, 422 BGC patients, 943 LC patients, 676 patients with NSCLC and 232 patients with SCLC. The respective efficacy populations comprised 540, 398, 832, 596, 205 patients.

In all 1927 patients enrolled, mean age was 63 years, 53% was female, lung tumor was the most frequent primary tumor (35% NSCLC, 12% SCLC), followed by breast- (13%), ovary- (8%) and colorectal tumor (6%). For 72% of the patients the current disease status was primary disease and for 61% of the patients the extent of disease was metastatic. Platinum containing chemotherapy was given to 67% of the patients, taxanes to 26% of the patients and alkylating agents to 18% of the subject (with all combinations possible).

EFFICACY RESULTS:

Percentage of responders amounted to 50% (69% for the alternative definition). Response rates without interference of transfusions were 42% (62% for the alternative definition), for the total study population.
Hemoglobin: After 28-35 days the Hb increased statistically significantly with a mean (SD) of 0.48 (1.75) g/dl and after 56-63 days with 1.18 (2.06) g/dl. Without interference of transfusions the Hb increased statistically significantly with 0.48 (1.72) g/dl after 28-35 days and with 1.31 (2.05) g/dl after 56-63 days.

During treatment with epoetin alfa 87% of the patients of the total study population reached an Hb level ≥ 11 g/dl and 68% reached a Hb level ≥ 12 g/dl. Without interference of transfusions these percentages amounted to 80% and 63%, respectively.

Hb increase of 1 g/dl at any time during epoetin alfa treatment was shown in 76% of the patients and an increase of 2 g/dl in 56% of the patients in the total study population. Without interference of transfusions these percentages amounted to 69% and 51%, respectively.

Subgroup analysis: For patients ≥70 group, results were similar to the results of the total study population. In the BGC group, response rates and Hb shifts seemed to be higher and time to response seemed to be shorter. In the LC group, response rates and Hb shifts seemed to be lower and time to response seemed to be longer, especially in the NCLC subgroup.

Blood transfusions: Between start of chemotherapy and end of the survey 34% of the patients received a blood transfusion, between start of epoetin alfa treatment and end of survey 28%. A blood transfusion at any time within 4 weeks after start of epoetin alfa treatment was given to 15% of the patients and 19% at any moment between 4 weeks after start of epoetin alfa treatment and end of the study.

Epoetin alfa treatment was initiated at a mean (SD) Hb of 10.4 (1.13) g/dl (median 10.5 g/dl) and for 79% epoetin treatment was started during the first three chemotherapy cycles. The time to response was 43 days (median). The last epoetin injection was given 20 days (average) after the last chemo cycle. The median duration of epoetin treatment was 10 weeks (95% CI: 11.38-12.09 weeks). Almost all patients (99.6%) started with a weekly epoetin dose of 40,000 IU , 7% had a dose increase and 3% had a dose decrease. Iron supplementation was given to 24% of the patients at any time from start of chemotherapy to end of the study. In LC, epoetin treatment seemed to start earlier and to be continued for a longer period, whereas in BGC it seemed to start later and to be given for a shorter period after the last chemo cycle.

SAFETY RESULTS: No unexpected safety concerns were found in this trial. Attribution to adverse events was assigned upon investigator assessment. A treatment-emergent adverse event was reported in 77% of the patients, with a total of 4892 TEAEs and 31% of patients reported any TESAE, with a total of 1181 TESAEs. Treatment-emergent thrombovascular AEs were reported for 8% of the patients. The most frequently mentioned (>= 5% of the patients) treatment-emergent adverse events after start of epoetin alfa treatment were fatigue (20%), nausea (13%), malignant neoplasm progression (9%), pyrexia (9%), dyspnea (8%), diarrhea (7%), malaise (7%), cough (6%), constipation (5%), vomiting (5%) and neuropathy (5%). During or after the survey 207 patients died. Although the causal relation to epoetin alfa was unknown for 10 deaths, none of the other reported deaths were assumed to have a causal relationship to the trial medication (189 not related and 8 doubtfully related). Disease progression was the most frequently reported cause of death (n=143). Six patients died due to a thrombovascular event: cerebrovascular accident (3), myocardial infarction (1) and pulmonary embolism (2); none of these events was assessed to be related to epoetin treatment.

STUDY LIMITATIONS: This study was an observational arm study. Study results cannot be compared with either placebo or a comparative treatment. Source data verification was performed on approximately 70% of all CRFs, which may have resulted in an underreporting of adverse events. As the epoetin alfa treatment is regarded as a supportive care treatment, quality of life data would have been valuable in the evaluation of the treatment. However, due to the observational character of the study and as data collection for quality of life questionnaires did not seem feasible, these data were not collected.

CONCLUSIONS: Epoetin alfa in cancer patients in the Netherlands is generally initiated at Hb levels in accordance to international guidelines for the management of chemotherapy induced anemia (CIA). Although, it must be noted that treatment guidelines have changed extensively over the years since study start. Treatment with once weekly epoetin alfa was generally able to correct chemotherapy-related anemia. Some differences in response rates and mean Hb-increase were observed in various sub-groups, possibly related to malignancy type and differences in impact on the erythropoeisis with cancer treatment choice. Evaluation of transferrin saturation or serum iron, during or prior to the epoetin alfa treatment did not seem common practice in the Netherlands. Moreover, iron supplementation is mostly given using oral preparations, whereas intravenous supplementation is recommended in guidelines for the management of CIA in case of iron deficiency.

Adverse events seem generally in line with the latest summary of product characteristics. Of note, thrombovascular TEAE's occurred in 152 patients (7.9%). None of the reported deaths during the study, were assessed as having a causal relationship to epoetin alfa upon investigator assessment.

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