Variation Assessment Report
Variation Type II C.I.13 [n°124] Procedure

EPREX/ERYPO
Epoetin alfa

Procedure Number: FR/H/0003/09-10
Variation Number: 13-14/II/124

Marketing Autorisation Holder: Janssen

Date: 20 March 2017

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ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	EPREX®/ERYPO®
Name of the active substance (INN, common name):	Epoetin alfa
Pharmaco-therapeutic group (ATC code)	B03XA01
Pharmaceutical form(s) and strength(s)	Solution for Injection in Pre-filled Syringes 2,000, 4,000, 10,000 & 40,000 IU/ml

Procedure number	FR/H/003/09-10, 13-14/II/124
Member States concerned	AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, LU, NL, PT, SE, UK

RMS contact person	**Name:** Tel: Email: @ansm.sante.fr France
Names of the assessors	**Clinical:** **Name(s):** Tel: Email: **@ansm.sante.fr** France

Nature of change/s requested	Modification of the Summary of Product Characteristics for Epoetin Alfa: Update to Sections 4.1: Extension of indication; 4.2: Posology; 4.8: Undesirable effects; 5.1: Pharmacodynamic properties.

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the FR/H/003/13-14/II/124 for EPREX®/ERYPO® (epoetin alfa), in the treatment of anemia (haemoglobin concentration of ≤ 10 g/dl) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS) is approvable. Overall conclusions were endorsed by , , and .

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The application concerns an update to the Summary of Product Characteristics (SmPC) and associated changes to the Patient Information Leaflet (PIL) of EPREX®/ERYPO® to add the new indication:
EPREX, ERYPO is indicated for the treatment of anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS).

This update involves changes in sections 4.1, 4.2, 4.8, 5.1 of the SmPC.

The MAH requests also 1 year of additional, non-cumulative data protection in this new indication in accordance with Paragraph 5 of Article 10 of Directive 2001/83/EC.

III. SCIENTIFIC DISCUSSION

III.1 Information on the medicinal product

The active substance of EPREX®/ERYPO® is epoetin alfa, a recombinant protein expressed in Chinese hamster ovary cells whose amino acid sequence is identical to human urinary glycoprotein hormone erythropoietin (EPO), and is supposed to be functionally indistinguishable from endogenous human EPO. EPO is a growth factor produced primarily by the kidney in response to hypoxia that stimulates red blood cell production. EPO receptors may be expressed on the surface of a variety of tumour cells.

Epoetin alfa is currently marketed under various names (EPREX®, ERYPO®, EPOPEN®, EPOXITIN® and GLOBUREN®), and dosage strengths as ampoules or prefilled syringes, each presentation being for single use.

EPREX®/ERYPO® received an original authorisation from the Committee for Proprietary Medicinal Products in June 1988 for the use in the treatment of adult chronic renal failure (CRF) patients on haemodialysis. EPREX®/ERYPO® is currently authorised for the following indications in Europe:

- Treatment of symptomatic anaemia associated with chronic renal failure (CRF):
    - in adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.
    - in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.

- Adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.
- Adults in a pre-donation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (Hb 10-13 g/dl [6.2 to 8.1 mmol/l], no iron deficiency) if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
- Non-iron deficient adults prior to major elective orthopaedic surgery having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (Hb 10-13 g/dl) who do not have an autologous pre-donation programme available and with expected moderate blood loss (900 to 1,800 ml).

III.2 Quality aspects

The MAH does not propose any modification of SmPC regarding quality aspects.

III.3 Non clinical aspects

The MAH does not propose any modification of SmPC regarding non clinical aspects.

III.4 Clinical aspects

III.4.1 Clinical pharmacology

The MAH does not propose any modification of SmPC regarding clinical pharmacology aspects.

III.4.2 Clinical efficacy

Myelodysplastic syndromes are clonal marrow stem-cell disorders, characterized by ineffective hemopoiesis leading to blood cytopenias, and by progression to acute myeloid leukemia (AML) in one third of patients. Fifteen percent of cases occur after chemotherapy or radiotherapy for a previous cancer; the syndromes are most common in elderly people. The pathophysiology involves cytogenetic changes with or without gene mutations and widespread gene hypermethylation at advanced stages. Clinical manifestations of MDS result from cytopenias (anemia, infection, and bleeding). Diagnosis is based on examination of blood and bone marrow showing blood cytopenias and hypercellular marrow with dysplasia, with or without excess of blasts. The natural course of MDS is highly variable, with survival ranging from a few weeks to several years. A number of classification systems have been developed to accommodate the broad spectrum of clinical outcomes of MDS, including the French-American-British (FAB), and the World Health

Organization (WHO) classification systems, as well as the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. Prognosis of the disease depends largely on the marrow blast percentage, number and extent of cytopenias, and cytogenetic abnormalities, which are grouped according to the International Prognostic Scoring System (IPSS) and the revised IPSS-R.

Anemia is a major contributor to the symptomatology of MDS and is associated with fatigue, weakness, shortness of breath, and comorbidity. The spectrum of the disease spans from chronic cytopenia-associated comorbidities, lasting for years in the lowest risk subgroups, to rapid progression to fatal acute myeloid leukemia (AML) in high-risk MDS. For patients with lower-risk MDS, cytopenias are a predominant feature and are associated with significant deterioration. Hematologic and quality of life improvement are important therapeutic goals.

Additional treatment options are needed for patients with earlier stages of MDS. Since the use of hypomethylating agents is associated with significant toxicity, these are currently utilized predominantly for patients with advanced stages of MDS. At the start of the EPOANE3021 study, agents approved in the European Union for the treatment of MDS, including Vidaza® (azacitidine) and Revlimid® (lenalidomide), were not approved for patients with low- or intermediate-1-risk MDS. Although Revlimid was subsequently approved in the European Union for use in low- or intermediate-1-risk MDS, the indication was restricted to a relatively narrow population: transfusion-dependent patients with an isolated deletion 5q cytogenetic abnormality.

Since anemia is the most common hematologic abnormality in patients with MDS, many studies have evaluated the role of ESAs in all subgroups of patients with MDS. The potential benefit of using an ESA is reduction of RBC transfusions, which have a negative impact on the lives of patients with MDS. Most of these patients have anemia and most develop an irreversible dependence on packed RBC transfusions. Iron overload after chronic transfusions may be also a contributing factor in the overall morbidity of the disease. The development of transfusion dependence and iron overload (as measured by serum ferritin) was associated with decreased overall survival and leukemia-free survival in addition to the known risk factors associated with MDS World Health Organization (WHO) subtype and cytogenetics. Further evaluations have indicated that a transfusion requirement of 2 units per month reduces the life expectancy of a patient with MDS by approximately 50%[1].

The results of several studies have demonstrated the effectiveness of epoetin alfa in improving hemoglobin concentrations and reducing transfusion requirements in patients with MDS. Although the benefit of erythropoietin-related transfusion reduction or avoidance has not been investigated in prospective, randomized, clinical studies, single-arm studies suggest that the median response duration for lower-risk patients with MDS is 59 to 89 weeks. The French MDS group reported that

[1] Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica. 2006;91:1588-1590.

the median duration of response was 20 months in erythropoietin-treated patients (EPOα, EPOβ, darbepoetinα) with low-risk MDS[2].

Since transfusion dependence negatively affects survival in patients with MDS, epoetin alfa treatment might reduce or avoid transfusion and ultimately provide a survival benefit. To date, no adequately designed studies have been conducted to address whether the response to erythropoietin treatment would translate to a survival benefit in patients with MDS. The French MDS group used the same International MDS Risk Analysis Workshop (IMRAW) database as was used to derive the original IPSS database[3] to derive a control group for their erythropoietin cases; patients who received erythropoietin with or without granulocyte colony-stimulating factor (G-CSF) had improved survival compared with subjects from the IPSS/IMRAW database who were untreated and growth factor-naïve[5].

The potential risks associated with treatment of MDS with an ESA include the risks associated with thrombotic vascular events (TVEs) and the potential for progression to AML. Antibody-mediated pure red cell aplasia (PRCA) has been rarely reported. Some studies have shown a consistent unexplained excess mortality in patients who have anemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Published findings from 2 studies that evaluated survival or local regional progression-free survival as primary endpoints indicated increased risks associated with treatment beyond the correction of anemia[4,5].

Previously, the results of prospective, randomized, placebo-controlled studies with erythropoietin suggested benefit for patients with MDS but did not provide sufficient robust evidence. Therefore, the MAH submitted in this procedure the EPOANE 3021 controlled study to evaluate treatment in this patient population.

III.4.2.1 Main study: EPOANE3021

EPOANE3021 study was a randomized, double-blind, placebo-controlled (2:1 randomization) Phase 3 study conducted to evaluate the efficacy and safety of epoetin alfa in anemic subjects with IPSS low- or intermediate-1-risk MDS requiring minimal or no transfusion. The inclusion of a 24-week double-blind treatment extension phase to obtain information on duration of response and use of a weight-based regimen of epoetin alfa were incorporated into the protocol based on feedback from ANSM. The open-label treatment extension phase was added for sites in Germany, Greece,

[2] Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008;111:574-582.
[3] Jädersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. Blood. 2005;106:803-811.
[4] Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. Lancet. 2003;362:1255-1260.
[5] 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 Oncol. 2005;23:5960-5972.

and Bulgaria based on discussions with the German Health Authority to allow for subjects to continue to receive study agent, that would not otherwise not be available to them, after the double-blind treatment period.

The primary objective was:

- To demonstrate that epoetin alfa treatment is better at improving anemia outcome (as evaluated by erythroid response – International Working Group [IWG] 2006 criteria; ie, an increase in hemoglobin by at least 1.5 g/dL or a relevant reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks; responses must last at least 8 weeks) in subjects with IPSS low- or intermediate-1-risk MDS compared with placebo through Week 24.

The secondary objectives were:

- For responders at Week 24, observe the duration of the response through Week 48.
- To assess the proportion of responders at Week 24 maintaining response through Week 48 (as measured by erythroid response).
- To compare time to first RBC transfusion, transfusion-free intervals, and number of RBC units transfused.
- To measure and compare changes in patient-reported outcome (PRO)/quality of life from baseline via the Functional Assessment of Cancer Therapy - Anemia/Fatigue (FACT-An) and EuroQol 5-dimension (EQ-5D) questionnaires.
- To collect medical resource utilization data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study).

Overall safety was also assessed.

III.4.2.1.1 Methods

This was a randomized, double-blind, placebo-controlled study conducted at multiple sites in Europe to evaluate the efficacy, safety, and effect on PRO/quality of life of epoetin alfa in adult anemic subjects with IPSS low- or intermediate-1-risk MDS requiring minimal or no transfusion.

The study included a 3-week pre-randomization phase and a 24-week double-blind treatment phase. At the end of the 24-week double-blind treatment phase, responders (as measured by erythroid response – IWG 2006 criteria) entered a 24-week double-blind treatment extension phase to measure the duration of response. Hereafter, these double-blind treatment phases will only be referred to as the treatment and treatment extension phases. Subjects completed an end-of-study visit 4 weeks after the last dose of study agent (Week 28 or Week 52), or 4 weeks after early withdrawal.

Eligible subjects were randomly assigned in a double-blind manner to receive either epoetin alfa or placebo in a 2:1 ratio, as follows:

- Group A: Starting dose of 450 IU/kg epoetin alfa (maximum total dose of 40,000 IU) administered subcutaneously once every week (planned n=between 83 and 106)
- Group B: Starting dose of a matching volume of placebo subcutaneously once every week (planned n=between 42 and 53)

Randomization was stratified according to transfusion requirement (yes vs. no) in the 8 weeks prior to baseline and serum erythropoietin level (at least 200 mU/mL vs. less than 200 mU/mL) during screening, ensuring equal distribution of these factors across treatment groups.

Throughout the study hemoglobin was measured every week. The dose of study agent could be withheld, decreased, or increased based on hemoglobin levels according to predefined dosage guidelines. A first dose increase was allowed only after the first 8 weeks of treatment. To maintain hemoglobin levels within the target range (baseline value plus 1.5 g/dL, up to 12 g/dL), study agent was withheld when the hemoglobin concentration exceeded 12 g/dL and not resumed until it dropped below 11 g/dL, regardless of the achievement of erythroid response. During the treatment extension phase, if the subject was found to have no erythroid response after the maximum allowed dose was received for at least 4 weeks, the subject was withdrawn from the study.

Throughout the study, subjects returned to the study center every 4 weeks for study assessments. The subjects' erythroid response was assessed at Week 8 and every 4 weeks thereafter, up to and including Week 24 or Week 48 for those subjects who were responders and continued in the treatment extension phase.

The total study duration for each subject was a maximum of 31 weeks or 55 weeks (including the 3-week pre-randomization phase). The study was considered completed with the last visit of the last subject participating in the study.

An independent Data Monitoring Committee (DMC) periodically evaluated unblinded safety and efficacy data.

Additionally, a Response Review Committee (RRC) was commissioned during the study by the sponsor to provide clinical review expertise for determination of erythroid response using the IWG 2006 criteria. The erythroid response review was performed independently of the sponsor and was completed on blinded data. The Statistical Analysis Plan (SAP), finalized before database lock, incorporated the RRC assessments of erythroid response into the primary and secondary endpoints and the planned analyses. The IWG 2006 response criteria do not include allowances for the protocol-required dose hold at a hemoglobin level >12.0 g/dL and subsequent dose decrease once level drops below 11 g/dL, which could lead to drops in hemoglobin levels below the defined response margin and not allow maintenance of the response over the required consecutive 8-week period. Potentially, this could result in inappropriately negative assessments of response in subjects who were otherwise responding to the therapy. Furthermore, it is possible that the effect of blood transfusions on hemoglobin levels could result in inappropriately positive assessments of response, if not assessed carefully for each subject. Since the application of the IWG 2006 response criteria

by investigators during the study may have varied given the above issues, the RRC was appointed to ensure a consistent approach to the response assessment.

At sites in Germany, Bulgaria, and Greece, an optional, open-label treatment phase was implemented to provide local treatment options for subjects with MDS, at the request of the health authorities/physicians in those countries. The key aspects and results of the open-label treatment phase will be reported separately.

Number of Subjects (planned and analyzed): The target number of subjects planned to participate in the study was between 125 and 159. A total of 186 potential subjects were screened for enrollment into the study and 130 subjects were randomly assigned to a treatment group (85 to epoetin alfa and 45 to placebo). Details of the number of subjects included in the analyses are presented below (Table 1).

Table 1: Details of the number of subjects included in the analysis

Data Sets Analyzed:	Placebo	Epoetin Alfa	Total
Intent-to-treat analysis set	45 (100%)	85 (100%)	130 (100%)
Modified intent-to-treat analysis set	45 (100%)	85 (100%)	130 (100%)
Safety analysis set	45 (100%)	85 (100%)	130 (100%)
Treatment extension phase	1 (2.2%)	39 (45.9%)	40 (30.8%)
Per-protocol analysis set	21 (46.7%)	32 (37.6%)	53 (40.8%)

Diagnosis and Main Criteria for Inclusion: Adult anemic men and women at least 18 years of age with: (i) a confirmed diagnosis of primary MDS (of any subtype) according to the World Health Organization (WHO) or French-American-British Cooperative Group (FAB) pathologic classification and (ii) an IPSS score indicating low- or intermediate-1-risk disease. Subjects were eligible if they had a screening and baseline hemoglobin level of ≤10.0 g/dL (≤10.5 g/dL if there had been blood transfusion(s) in the 2 weeks prior to screening, or between screening and baseline), screening serum erythropoietin concentration of less than 500 mU/ml, RBC transfusion requirement of ≤4 RBC units over the 8 weeks before randomization, and adequate iron stores.

Subjects with secondary MDS, or with anemia attributable to factors other than MDS, those who received therapy with any erythropoiesis-stimulating agent (ESA) in the 8 weeks before randomization, and those with a history of venous thrombosis or arterial thrombosis within the previous 6 months, were excluded. Other exclusion criteria included: uncontrolled hypertension, history of pure red cell aplasia (PRCA) and/or antibody against erythropoietin, or having received iron chelation therapy for 6 months or more at screening for iron overload caused by blood transfusion.

Duration of Treatment: Epoetin alfa or placebo was administered once weekly for 24 weeks in the treatment phase. Subjects who had an erythroid response at Week 24 continued to receive epoetin alfa once weekly through Week 48 in the treatment extension phase. If the subject did not have an erythroid response after having received the maximum allowed dose for at least 4 weeks during the treatment extension phase, study agent was discontinued and the subject was withdrawn from the study.

Criteria for Evaluation: Hemoglobin concentrations were measured at screening, at baseline, and at least once every week during the treatment phase and the treatment extension phase before study agent administration. A full hematologic evaluation and evaluation for disease progression (according to IWG 2006 criteria) including acute myeloid leukemia (AML) or malignancy were performed every 4 weeks.

Erythroid response was assessed by the investigator at Week 8 and every 4 weeks thereafter. The investigators used the hemoglobin measured at the visit for their assessment of erythroid response, and did not take into account the continuous 8-week period before the visit. The RRC used the IWG 2006 criteria to assess blinded erythroid response data for each subject, taking into account factors such as RBC transfusions and protocol-specified dose adjustments. The RRC assessed whether erythroid response was demonstrated for a period of at least 8 weeks at any time up to Week 24, defined the week that erythroid response became apparent and the last week that erythroid response was demonstrable for the entire duration of study participation, and if erythroid response was demonstrable at Week 24, provided the response duration.

Detailed information was collected on all RBC transfusions administered to the subject throughout the study. Two PRO/quality of life instruments (FACT-An and EQ-5D) were completed by the subject at baseline, Week 24 (all subjects) and Week 48 (subjects enrolled in the treatment extension phase).

The primary efficacy parameter, as defined in the SAP, was defined by the demonstration of:

- Erythroid response at any time during the first 24 weeks of the study as assessed by the RRC.

Secondary efficacy parameters, as defined in the SAP, were:

- Erythroid response at Week 24 as assessed by the RRC;
- Erythroid response as recorded in the case report form (CRF) at Week 24;
- Duration of response (days) as defined by the assessment of the RRC for subjects who responded at any time during the first 24 weeks of the study;
- Proportion of responders at Week 48, based on the RRC assessment of erythroid response. Responders at Week 48 were subjects who responded at Week 24, continued the study treatment, and maintained the response status through Week 48;
- Time to first RBC transfusion (days);
- Transfusion-free days;
- Number of RBC units transfused;
- Change from baseline in PRO/quality of life (as assessed with the FACT-An and EQ-5D).

Safety assessment was based on reported adverse events, thrombotic vascular events (TVEs), relapse after hematologic improvement and disease progression, bone marrow examination, loss of response to study agent, clinical laboratory tests, erythropoietin antibody tests, vital sign measurements, and physical examinations.

Medical resource utilization and health economics data associated with medical encounters were collected throughout the study.

Statistical Methods: Sample size calculations were based on the assumption that the proportion of subjects who were responders at Week 24 would be 35% for the epoetin alfa group and 10% for the placebo group. Using a 2:1 ratio randomization and a Fisher exact test with a 0.05 2-sided significance level, corrected for a 10% dropout rate, ≥125 subjects (83 in the epoetin alfa group, 42 in the placebo group) needed to be included in the study to achieve at least 80% power.

All statistical tests were 2-sided at a significance level of 0.05. Baseline for all analyses was the Day 1 visit (randomization and first dose of study agent). The modified intent-to-treat (mITT) analysis set was defined as all subjects who received at least 1 dose of study agent and had at least 1 post-baseline efficacy assessment; this analysis set was used for all efficacy analyses.

The hypothesis in this study was that treatment with epoetin alfa successfully improves anemia outcome in subjects with IPSS low- or intermediate-1-risk MDS. The primary efficacy parameter (demonstration of erythroid response at any time during the first 24 weeks of the study as assessed by the RRC) was summarized by frequency and percentage and the difference between treatment groups was tested using the Fisher exact test. Erythroid response rates in the treatment groups were also summarized by stratification factors and IPSS risk category at screening and compared using the Cochran-Mantel-Haenszel test.

Secondary endpoints were summarized using frequencies and percentages, continuous summary statistics (mean [standard deviation (SD)], median, range, and 95% confidence interval [CI] for the mean), and standard survival analysis methods including Kaplan-Meier product-limit survival curve estimates, log-rank tests, and proportional hazard regression models. Between-group comparisons were tested using the Fisher exact test or Wilcoxon 2-sample test, as appropriate. The Wilcoxon signed rank test was used to analyze change from baseline scores.

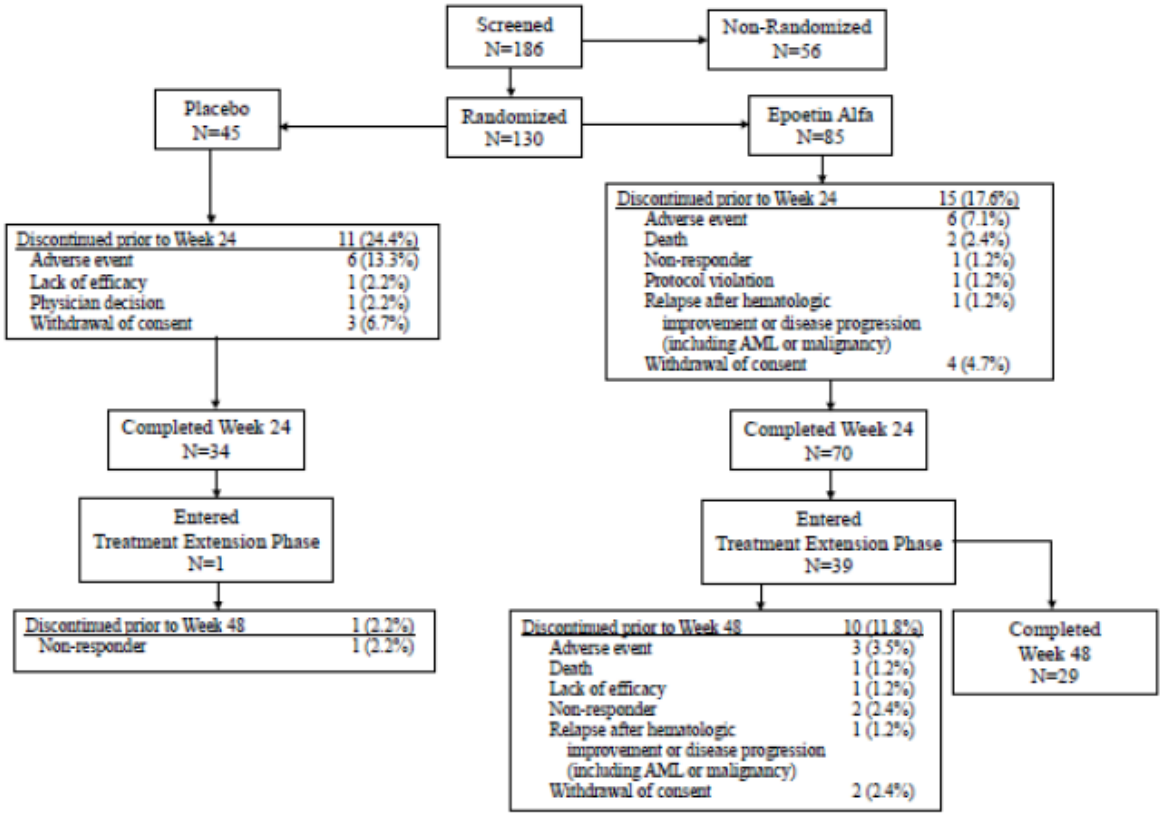
Safety data were summarized descriptively. The safety analysis set was defined as all subjects who were randomly assigned to a treatment group and received at least 1 dose of study agent. Adverse events were summarized by treatment group, system organ class and preferred term. The numbers of subjects with a TVE were summarized by treatment group.

III.4.2.1.2 Results

III.4.2.1.2.1 Subject Disposition

A total of 186 potential subjects were screened for enrollment into the study and 130 subjects were randomly assigned to a treatment group (85 to epoetin alfa and 45 to placebo; Figure 2).

Figure 2: Subject Disposition in study EPOANE 3021



The 56 non-randomized subjects were either screen failures (51) or were not assigned to a treatment group (1 subject died and 4 withdrew consent). A higher percentage of subjects in the placebo group discontinued prior to Week 24 compared with the epoetin alfa group: 11 (24.4%) vs. 15 (17.6%). Of the subjects who completed through Week 24, 1 subject in the placebo group and 39 subjects in the epoetin alfa group entered the 24-week extension phase. A total of 11 subjects (1 in the placebo group and 10 in the epoetin alfa group) discontinued during the 24-week extension phase and 29 subjects in the epoetin alfa group completed the 24-week extension phase. The most common reasons for discontinuation at any time during the study (ie, prior to Week 24 or after Week 24) in both treatment groups were adverse events and withdrawal of consent.

III.4.2.1.2.2 Demographic and Baseline Characteristics in EPOANE3021 study

Baseline demographics were comparable between the treatment groups. Overall, the median age was 75 years, 54.6% were men, and the median BMI was 26.67 kg/m^2. There was a higher percentage of subjects with an IPSS risk category of intermediate-1 in the epoetin alfa group (57.6% vs. 48.9%); however, there was no statistically significant difference between the treatment groups with respect to IPSS risk category (p=0.355) when compared using the Fisher exact test, 2-sided (see Table 2). Overall, 50.0% of subjects had an ECOG score of 1 (restricted but ambulatory).

For the MDS subtype according to WHO classification, the majority of all subjects had 1 of 3 subtypes: 43.8% were classified as refractory cytopenia with multilineage dysplasia (RCMD)

(42.4% of subjects in the epoetin alfa group, 46.7% of subjects in the placebo group), 13.8% as refractory anemia (RA) (8.2% and 24.4%, respectively), and 13.1% as RCMD with ringed sideroblasts (RCMD-RS) (14.1% and 11.1%, respectively; Table 2).

For the MDS subtype according to FAB classification, the majority of all subjects (62.3%) were classified as RA (54.1% of subjects in epoetin alfa group, 77.8% of subjects in placebo group) and 21.5% of all subjects were classified as refractory anemia with ringed sideroblasts (RARS) (24.7% and 15.6%, respectively; Table 2).

Table 2: Demographics and Baseline Characteristics in EPOANE 3021 study

	Placebo	Epoetin Alfa	Total
MDS subtype according to WHO classification			
N	44	82	126
RA	11 (24.4%)	7 (8.2%)	18 (13.8%)
RARS	2 (4.4%)	9 (10.6%)	11 (8.5%)
RCMD	21 (46.7%)	36 (42.4%)	57 (43.8%)
RCMD-RS	5 (11.1%)	12 (14.1%)	17 (13.1%)
RAEB-1	1 (2.2%)	10 (11.8%)	11 (8.5%)
RAEB-2	0	1 (1.2%)	1 (0.8%)
MDS-U	0	1 (1.2%)	1 (0.8%)
5q-	3 (6.7%)	2 (2.4%)	5 (3.8%)
AML	0	0	0
Not available	1 (2.2%)	4 (4.7%)	5 (3.8%)
MDS subtype according to FAB classification[b]			
N	44	82	126
RA	35 (77.8%)	46 (54.1%)	81 (62.3%)
RARS	7 (15.6%)	21 (24.7%)	28 (21.5%)
RAEB	1 (2.2%)	11 (12.9%)	12 (9.2%)
RAEB-t	0	0	0
CMML	1 (2.2%)	4 (4.7%)	5 (3.8%)
AML	0	0	0
Not available	0	0	0
IPSS risk category[c]			
N	45	85	130
Low = 0	23 (51.1%)	35 (41.2%)	58 (44.6%)
Intermediate-1 = 0.5 to 1.0	22 (48.9%)	49 (57.6%)	71 (54.6%)
Intermediate-2 = 1.5 to 2.0	0	0	0
High = ≥2.5	0	0	0
Missing	0	1 (1.2%)	1 (0.8%)
p-value		0.355	
ECOG score			
N	45	85	130
0 - Fully active	20 (44.4%)	35 (41.2%)	55 (42.3%)

1 - Restricted but ambulatory	23 (51.1%)	42 (49.4%)	65 (50.0%)
2 - Ambulatory	2 (4.4%)	8 (9.4%)	10 (7.7%)
3 - Capable but confined to bed/chair	0	0	0
4 - Completely disabled	0	0	0
Missing	0	0	0

[a] BMI kg/m^2 ; weight (kg)/((height (cm)/100)* (height (cm)/100))

[b] According to FAB, CMML subjects were marked as MDS subtype not available in the WHO classification.

[c] One subject was missing their IPSS category at screening. The p-value for treatment group differences are based on the Fisher exact test, 2-sided.

5q- = myelodysplastic syndromes associated with isolated del(5q); AML = acute myeloid leukemia; BMI = body mass index; CI = confidence interval; CMML = chronic myelomonocytic leukemia; FAB = French-American-British; IPSS = International Prognostic Scoring System; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndromes; MDS-U = myelodysplastic syndrome, unclassified; RA = refractory anemia; RARS = refractory anemia with ringed sideroblasts; RAEB = refractory anemia with excess blasts; RAEB-t = refractory anemia with excess blasts in transformation; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia with ringed sideroblasts; SD = standard deviation; WHO = World Health Organization.

Assessor's comment

Randomisation has well balanced the current demographic baseline characteristics, but there are some discrepancies between Eprex and placebo arms regarding myelodysplastic syndrome subtypes, some concomitant therapy and ongoing pathologies which should be further discussed in term of impact on the response to treatment.

For the MDS subtype according to WHO classification: 43.8% were classified as refractory cytopenia with multilineage dysplasia (RCMD) (42.4% of subjects in the epoetin alfa group, 46.7% of subjects in the placebo group), 13.8% as refractory anemia (RA). A higher rate of RA was found in the placebo group (8.2% vs 24.4%). Also, higher rate of RARS, RA with ringed sideroblasts (4.4% vs 10.6%) and RAEB-1, RA with excess blasts (2.2% and 11.8%) were observed in epoietin alfa group.

For the MDS subtype according to FAB classification, higher rates of RA in placebo and of RARS and RAEB in epoetin alfa were confirmed.

Thus, higher RA with excess blasts without transformation were found in the epoetin alfa group. However, the number of patients with RAEB seemed not associated with a significant excess of blast as the IPPS risk category was not affect in the randomization.

Finally, the population included was in accordance with the pathology and the stages of the disease.

However, the prognostic score IPPS[6] was revised from the start of the study (23 June 2011) and its analysis in March 2016 and called IPPS-R. Changes in patient's distribution in this score, in particularly between score IPSS-R intermediate and high have been observed[9]. The interpretation of the data could be modified. In order to clarify the data at the baseline and to confirm epoietin alfa in SMD low and intermediate risk, the MAH could update the distribution of the patients regarding the score IPPS-R **(OC)**.

Among the subjects who completed through Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group entered the 24-week extension phase. Thus, efficacy assessment was focused on the first 24 weeks, which was the primary objective.

Baseline hemoglobin values and RBC transfusion-related information in the 8 weeks prior to baseline for the mITT analysis set are provided in Table 3. The baseline mean hemoglobin values were similar between the 2 treatment groups. The percentage of subjects with RBC transfusions and number of RBC units per subject transfused in the 8 weeks before baseline were comparable between the 2 treatment groups.

Table 3: Baseline Hemoglobin and Transfusions Prior to Baseline

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Hemoglobin (g/dL) Baseline (Day 1) N	45	85
Mean (SD)	9.18 (0.848)	9.12 (0.939)
Median	9.4	9.3
Range	(6.9, 10.5)	(6.8, 11.0)
(Lower 95% CI, Upper 95% CI for the Mean)	(8.93, 9.44)	(8.92, 9.32)
Transfusion in 8 Weeks Prior to Baseline Visit		
N	45	85
Number of subjects with transfusions (%)	22 (48.9%)	44 (51.8%)
Number of transfusion events prior to baseline visit	36	75
Total RBC units prior to baseline visit	53	114
RBC units required per subject receiving transfusions	2.4	2.6

Assessor's comment

Randomization of the study has well balanced concerning the haemoglobin but these data should be taken with cautions as the level of haemoglobin should be discussed regarding transfusions data. Concerning the number of transfusion, it was required in the inclusion criteria that RBC transfusion requirement should not exceed 4 RBC units over the 8 weeks before randomization.

[6] Greenberg PL et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65.

The RMS recognizes that there is no consensus conclusions in defining persons who are RBC-transfusion-dependent and independent. For example, the WHO classification defined RBC-transfusion-dependence as received ≥1U RBC ≤8 weeks averaged over 4 months. IWG in MDS in 2000 proposed different criteria: ≥1 RBC-transfusion for a hemoglobin level ≤90g/l with no surveillance interval specified. However, the MAH should specified the number of subjects receiving less than 2 RBC units (≤ 2) and between 2 and 4 units in 8 weeks prior to baseline visit in order to better document the efficacy of epoietin alfa regarding the severity of the disease of these patients **(OC)**.

Baseline bone marrow characteristics are summarized in Table 4.

	Placebo	Epoetin Alfa	Total
Analysis set: full analysis set	45	85	130
Bone marrow aspirate			
Iron Stores			
N	45	85	130
Adequate	40 (88.9%)	75 (88.2%)	115 (88.5%)
Inadequate	0	4 (4.7%)	4 (3.1%)
Missing	5 (11.1%)	6 (7.1%)	11 (8.5%)
Percent myeloblasts			
N	45	85	130
No blasts	2 (4.4%)	4 (4.7%)	6 (4.6%)
≤5%	43 (95.6%)	71 (83.5%)	114 (87.7%)
>5%	0	10 (11.8%)	10 (7.7%)
Percent ringed sideroblasts			
N	45	85	130
No ringed sideroblasts	10 (22.2%)	12 (14.1%)	22 (16.9%)
<15%	26 (57.8%)	51 (60.0%)	77 (59.2%)
≥15%	9 (20.0%)	22 (25.9%)	31 (23.8%)

Dysplasia: Yes[a]			
N	44	84	128
Erythroid	41 (91.1%)	75 (88.2%)	116 (89.2%)
Granulocyte	25 (55.6%)	53 (62.4%)	78 (60.0%)
Megakaryocyte	22 (48.9%)	53 (62.4%)	75 (57.7%)
Bone marrow biopsy			
Cellularity type[b]			
N	45	85	130
Hypercellular	9 (20.0%)	11 (12.9%)	20 (15.4%)
Normocellular	2 (4.4%)	3 (3.5%)	5 (3.8%)
Hypocellular	0	5 (5.9%)	5 (3.8%)
Missing	34 (75.6%)	66 (77.6%)	100 (76.9%)
Percent cellularity[b]			
N	7	8	15
Mean (SD)	62.1 (19.97)	60.0 (19.09)	61.0 (18.82)
Median	70.0	57.5	60.0
Range	(20, 80)	(35, 90)	(20, 90)
(Lower 95% CI, upper 95% CI for the mean)	(43.7, 80.6)	(44.0, 76.0)	(50.6, 71.4)
Percent myeloblasts			
N	45	85	130
No blasts	28 (62.2%)	61 (71.8%)	89 (68.5%)
≤5%	14 (31.1%)	22 (25.9%)	36 (27.7%)
>5%	3 (6.7%)	2 (2.4%)	5 (3.8%)

[a] Subjects could be counted in multiple categories. [b] Sites entered bone biopsy results as cellular type or percent cellularity. SD = standard deviation.

Assessor's comment

Globally, the bone marrow baseline characteristics were similar with higher rate of excess blast >5% in the epoietin alfa group bone marrow aspirate but not confirmed in the bone marrow biopsy.

Notable ongoing medical disorders at study entry included: hypertension (49.4% of subjects in the epoetin alfa group, 62.2% in the placebo group); diabetes mellitus (preferred terms combined for diabetes mellitus and Type 2 diabetes; 25.9% and 15.6%, respectively), dyslipidemia (preferred terms combined for hypercholesterolemia, dyslipidemia, and hyperlipidemia; 22.4% and 15.6%, respectively); osteoarthritis (15.3% and 13.3%, respectively); renal failure (preferred terms combined for renal failure and renal failure chronic; 10.6% and 11.1%, respectively); osteoporosis (5.9% and 11.1%, respectively); coronary artery disease (7.1% and 4.4%, respectively); myocardial ischemia (4.7% and 0, respectively); angina pectoris (3.5% and 2.2%, respectively); vitamin B12 deficiency (1.2% and 4.4%, respectively); and iron deficiency (1.2% and 2.2%, respectively).

Assessor's comment

As previously stated, descriptive discrepancies (hypertension, type2 diabetes or dyslipidemia…) should be further discussed in term of possible impact on the treatment outcome (efficacy and safety) **(OC)**.

III.4.2.1.2.3 Prior and Concomitant Therapies

During the 8 weeks prior to the baseline visit, 44 (51.8%) subjects in the epoetin alfa group and 22 (48.9%) subjects in the placebo group had received RBC transfusions (Table 3).
Concomitant therapies of clinical interest are summarized by WHO Drug classification and preferred term (version March 2011) in Table 4.

Table 4: Concomitant therapies of clinical interest

(Study EPOANE3021: Intent-to-Treat Analysis Set)

Drug classification [a]	Preferred Term	Placebo	Epoetin Alfa
Analysis set: intent-to-treat		45	85
Platelet Aggregation Inhibitors Excl. Heparin	Antithrombotic agents	10 (22.2%)	23 (27.1%)
Heparin Group	Antithrombotic agents	2 (4.4%)	10 (11.8%)
Vitamin K Antagonists	Antithrombotic agents	1 (2.2%)	6 (7.1%)
Direct Thrombin Inhibitors	Antithrombotic agents	0	1 (1.2%)
Glucocorticoids	Corticosteroids for systemic use	13 (28.9%)	17 (20.0%)
Ace Inhibitors, Plain	Agents acting on the renin-angiotensin system	7 (15.6%)	15 (17.6%)
Angiotensin II Antagonists, Plain	Agents acting on the renin-angiotensin system	15 (33.3%)	12 (14.1%)
Angiotensin II Antagonists and Diuretics	Agents acting on the renin-angiotensin system	1 (2.2%)	5 (5.9%)
Ace Inhibitors and Diuretics	Agents acting on the renin-angiotensin system	0	2 (2.4%)
Angiotensin II Antagonists and Calcium Channel Blockers	Agents acting on the renin-angiotensin system	0	1 (1.2%)
Renin-Inhibitors	Agents acting on the renin-angiotensin system	0	1 (1.2%)
Thyroid Hormones	Thyroid therapy	2 (4.4%)	9 (10.6%)
Iron Bivalent, Oral Preparations	Antianemic preparations	2 (4.4%)	8 (9.4%)
Folic Acid and Derivatives	Antianemic preparations	9 (20.0%)	7 (8.2%)
Other Antianemic Preparations[b]	Antianemic preparations	3 (6.7%)	3 (3.5%)
Vitamin B12 (Cyanocobalamin and Analogues)	Antianemic preparations	3 (6.7%)	3 (3.5%)
Iron Trivalent, Parenteral Preparations	Antianemic preparations	0	2 (2.4%)
Iron In Combination With Folic Acid	Antianemic preparations	0	1 (1.2%)
Iron In Other Combinations	Antianemic preparations	0	1 (1.2%)
Vitamin B1 In Combination With Vitamin B6 and/or Vitamin B12	Vitamins	3 (6.7%)	1 (1.2%)
Iron Chelating Agents	All other therapeutic products	5 (11.1%)	4 (4.7%)
Coxibs	Antiinflammatory and antirheumatic products	1 (2.2%)	3 (3.5%)

Note: Concomitant medications are defined as those with stop dates on or after the Day 1 visit date, or ongoing.
[a] Medications coded using Who Drug C_DDE dictionary, version March 2011.
[b] All were erythropoiesis-stimulating agents started after subjects discontinued from the study. Darbepoetin alfa received by 1 subject in the epoetin alfa group; all other subjects received epoetin alfa.

Assessor's comment

Globally, prior and concomitant therapies used were similar in the two group except use of antithrombotic agents which were higher in the epoetin alfa group and use of glucorticoïds, angiotensin II, vitamin B1 and iron chelating agents in placebo group.

The MAH should discuss the higher use of antithrombotic agents regarding the safety evaluation (e.g. higher TVE in epoetin alfa group) **(OC).**

III.4.2.1.2.4 Protocol Deviations in EPOANE3021 study

Of the 130 subjects in the ITT analysis set, 77 (59.2%) had a major protocol deviation within the first 24 weeks. A higher percentage of subjects in the epoetin alfa group had a major protocol deviation compared with the placebo group (62.4% vs. 53.3%; Table 5).

Table 5: Major Protocol Deviations Within First 24 Weeks in study EPOANE 3021: intent-to-treat Analysis Set

	Placebo	Epoetin Alfa
Analysis set: intent-to-treat	45	85
Subjects reporting at least 1 major protocol deviation within first 24 weeks	24 (53.3%)	53 (62.4%)
Subjects with major protocol deviations[a]:		
Received the wrong treatment or incorrect dose[b]	16 (35.6%)	40 (47.1%)
Entered the study but entry criteria not met	10 (22.2%)	17 (20.0%)
Other	8 (17.8%)	7 (8.2%)
Received excluded concomitant treatment	0	1 (1.2%)

[a] Subjects may be counted in more than 1 major protocol deviation class within the first 24 weeks.

[b] In the category "Received wrong treatment or incorrect dose" are captured deviations in medication dosing from dose adjustment rules and 2 subjects who received injections from the wrong treatment group (received placebo instead of epoetin alfa).

More than 50% of subjects in each treatment group had at least 1 major protocol deviation within the first 24 weeks of the study, with the highest percentage of these related to the dosing regimen.

Most of the deviations related to dosing regimen occurred early in the study. These deviations were addressed at an individual site level as well as through study-wide communications and training and implementation of additional tools to help the sites follow the dose modification rules. Weight-based dosing, rather than fixed doses as recommended by treatment guidelines for MDS[7] was used in this study along with dose modification rules based on weekly hemoglobin measurements which aimed to deliver the minimal effective dose to the subject throughout the study. The weight-based dosing, as well as the dose modification rules proved to be a challenge to the sites. These issues with study design, along with the fact that every dosing error in the first 24 weeks was considered a

[7] Fenaux P, Haase D, Sanz GF, et al. on behalf of the ESMO Guidelines Working Group: Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Supp 3):iii57-69.

major protocol deviation, provide some explanation for the high number of major protocol deviations related to dosing. Despite these deviations, the study represents a controlled evaluation of epoetin alfa in treatment of anemia in subjects with MDS, and the protocol deviations related to dosing per se are consistent with MDS treatment recommendations and the challenges that come with dose adjustment rules applied on a weekly basis.

Eligibility criteria were stringent in the first version of the protocol and not consistent with clinical practice in countries that participated in the study and in real-life MDS patients, which led to an amendment to the protocol. The significant number of major protocol deviations on eligibility criteria, even though formally deviating from the approved study protocol, in some cases would not exclude some subjects based on the last amended protocol version and in most cases would not exclude the subject from the population targeted for epoetin alfa therapy in clinical practice.

Analyses performed using both the mITT and PP analysis sets had similar results; therefore, these major protocol deviations related to dosing and included study population did not significantly alter the outcome of the study.

In summary, the major protocol deviations in the first 24 weeks of this study varied in nature and were not considered to have any clinically relevant impact on data integrity.

Assessor's comment

There is a high rate of major protocol deviations. According to the MAH, these deviations are mainly due to dosing problems. The MAH should be more specific about the deviations to the dose. The MAH should provide for each group, the number of subjects who received an incorrect starting dose (at baseline) and the number of subjects who received an incorrect dose at any following visit up to week 24 **(OC)**.

In the protocol, the Hb levels were measured at screening, at baseline, and at least once every week during the entire period. Subjects could visit the study center once per week for hemoglobin testing, followed by study agent administration. Alternatively, weekly hemoglobin testing could be performed at home or at a local laboratory. Upon request, the subject or caregiver using a portable photometer provided by the sponsor could perform Hb measurement. For a given subject, preferably the same method for measuring hemoglobin was to be used throughout the study.

It was described in the report of protocol deviations some discrepancies as "Hb measured in external not approved laboratory and no normal range provided". Thus, the MAH should discuss the impact of protocol deviations concerning Hb level measurement in order to assume the reliability of the main criterion. In addition, the MAH should provide erythroid response regarding to the detail of patients whom the hemoglobin was measured in study center, local laboratory or using the portable photometer **(OC)**.

III.4.2.1.2.5 Extent of Exposure in EPOANE3021 study

Subjects in both treatment groups received a starting dose of 450 IU/kg (first 8 weeks) adjusted to a maximum of 1,050 IU/kg (any time after Week 8). The maximum total dose was 40,000 IU administered subcutaneously once every week during the first 8 weeks of treatment and 80,000 IU once every week after Week 8. The median weekly dose was 730.4 IU/kg (range: 343, 946) in the epoetin alfa group and 850.0 IU/kg (range, 404, 910) in the placebo group. In the safety analysis set, the percent of the subjects in the epoetin alfa group who had a decrease in dose was 54.1% compared with 20.0% of subjects in the placebo group. Exposure to study agent was the same in the mITT analysis set.

For subjects in the mITT analysis set, the mean (SD) duration of treatment for the epoetin alfa group was 30.9 (14.04) weeks and 21.3 (6.38) weeks for the placebo group. Note that per protocol, all subjects were to continue treatment until Week 24 regardless of their erythroid response status. The mean (SD) duration of treatment for subjects in the PP analysis set was similar to that observed in the mITT analysis set; 31.2 (14.30) weeks in the epoetin alfa group compared with 19.6 (7.18) weeks in the placebo group.

Table 6: Exposure

(Study EPOANE3021: Safety Analysis Set)

	Placebo	Epoetin Alfa
Analysis set: safety	45	85
Number of weekly doses, n (%)		
1	0	2 (2.4%)
5	1 (2.2%)	1 (1.2%)
6	1 (2.2%)	0
7	2 (4.4%)	1 (1.2%)
9	1 (2.2%)	2 (2.4%)
10	0	1 (1.2%)
11	0	1 (1.2%)
12	0	2 (2.4%)
13	1 (2.2%)	0
15	1 (2.2%)	1 (1.2%)
16	1 (2.2%)	0
17	2 (4.4%)	2 (2.4%)
18	0	3 (3.5%)
19	1 (2.2%)	0
20	0	1 (1.2%)
21	0	1 (1.2%)
22	1 (2.2%)	3 (3.5%)
23	1 (2.2%)	5 (5.9%)
24	7 (15.6%)	5 (5.9%)
25	23 (51.1%)	18 (21.2%)
26	0	3 (3.5%)

28	1 (2.2%)	1 (1.2%)
29	0	1 (1.2%)
30	1 (2.2%)	1 (1.2%)
31	0	3 (3.5%)
32	0	1 (1.2%)
34	0	1 (1.2%)
37	0	2 (2.4%)
38	0	1 (1.2%)
39	0	1 (1.2%)
40	0	2 (2.4%)
41	0	1 (1.2%)
42	0	1 (1.2%)
44	0	3 (3.5%)
45	0	1 (1.2%)
46	0	5 (5.9%)
47	0	4 (4.7%)
48	0	1 (1.2%)
49	0	3 (3.5%)
Number of subjects with dose increases, n (%)	40 (88.9%)	67 (78.8%)
Number of subjects with dose decreases, n (%)	9 (20.0%)	46 (54.1%)
Average weekly dose (IU/kg)		
N	45	85
Mean (SD)	771.7 (144.61)	683.1 (193.58)
Median	850.0	730.4
Range	(404, 910)	(343, 946)
(Lower 95% CI, Upper 95% CI for the Mean)	(728.3, 815.2)	(641.3, 724.9)
Mode weekly dose (IU/kg)[a]		
N	45	85
Mean (SD)	897.5 (260.35)	745.6 (306.86)
Median	1050.0	787.5
Range	(450, 1050)	(338, 1050)
(Lower 95% CI, Upper 95% CI for the Mean)	(819.3, 975.7)	(679.4, 811.8)

Note: One subject had a dose distribution that was multi-modal, so the mode of 787.5 IU/kg was used for the summary statistics since it was closest to the mean and median dose.
Mode weekly dose refers to the most frequently occurring dose.
CI = confidence interval; SD = standard deviation.

Assessor's comment

This table 6 seems to reflect the total number of doses actually received by subjects through their entire participation in the study. The MAH should also provide for both arms, the number of subjects who actually received 25 doses from day 1 to week 24 (one dose per week as recommended in the SmPC). Moreover, the MAH should provide the distribution of the number of doses received by the responders in the Eprex arm within the first 24 weeks of the study. The same should be provided for the extension phase **(OC).**

III.4.2.1.2.6 Immunogenicity Results

At screening and at Week 48, no subjects in the mITT analysis set in either treatment group were positive for antibodies to erythropoietin; 1 (1.2%) subject in the epoetin alfa group was positive for antibodies to erythropoietin at Week 24 and led to permanent discontinuation of study agent. For this subject, there were no signs of PRCA reported in the bone marrow; serum erythropoietin

remained detectable and reticulocytes were normal at the last available measurement. No subjects in the PP analysis set were positive for antibodies to erythropoietin at any time point.

Assessor's comment

PRCA is a very rare adverse event, which is strongly followed for all EPO.

There is no relevant data allowing assuming an increased risk of PRCA in EPO treated MDS.

III.4.2.1.2.7 Efficacy Results

The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received. The mITT analysis set was defined as randomized subjects who received at least 1 dose of study agent and had at least 1 post-baseline efficacy assessment. The ITT and the mITT analysis sets were identical; therefore, the mITT analysis set was used for all efficacy analyses.

A PP analysis was performed, as described in the protocol, since there were a substantial number of subjects with protocol deviations (eg, more than 10%). The PP analysis set was defined as all subjects who completed the 24-week treatment phase or terminated the study before Week 24, received all doses of treatment as required by protocol, and had no major protocol deviations during the first 24 weeks.

A summary analysis sets used in the efficacy analyses is presented in Table 7.

Table 7: Efficacy Data Sets

	Placebo	Epoetin Alfa	Total
Intent-to-treat analysis set[a]	45 (100%)	85 (100%)	130 (100%)
Modified intent-to-treat analysis set[b]	45 (100%)	85 (100%)	130 (100%)
Per-protocol analysis set[c]	21 (46.7%)	32 (37.6%)	53 (40.8%)

[a] The intent-to-treat analysis set consists of all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received. Percentages are calculated using the counts of intent-to-treat subjects as the denominator.

[b] The modified intent-to-treat analysis set consists of subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.

[c] The per-protocol analysis set consists of all subjects who completed the 24-week treatment phase or had early termination before Week 24, had received all doses of treatment as required by protocol, and had no major protocol deviations during the first 24 weeks.

III.4.2.1.2.7.1 Primary Efficacy Analysis

The overall comparison of the erythroid response at any time during the first 24 weeks of the study showed a statistically significant difference between the treatment groups in the mITT analysis set. In the epoetin alfa group, 27 (31.8%) subjects had an erythroid response at any time during the first 24 weeks compared with 2 (4.4%) subjects in the placebo group ($p<0.001$ using a Fisher's exact test, 2-sided). When the analysis was performed stratifying by either the stratification variables or the IPSS risk categories at screening, there was also a statistically significant difference between the treatment groups (Table 8). All of the responding subjects were in the strata with serum erythropoetin less than 200 mU/mL during screening.

Additionally, there were 2 subjects who responded late in the study and showed response at Week 24 but did not have 8 weeks of response by Week 24.

Table 8: Erythroid Response at Any Time during the First 24 Weeks in study EPOANE 3021: modified ITT Analysis Set

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Subjects with erythroid response[a] at any time during the first 24 weeks of study	2 (4.4%)	27 (31.8%)
p-value [b]		<0.001
Subjects with erythroid response by stratification group		
Strata 1: Transfusion="No" and serum erythropoietin level less than 200 mU/mL[c]	1 (5.0%)	18 (47.4%)
Strata 2: Transfusion="Yes" and serum erythropoietin level less than 200 mU/mL[c]	1 (5.3%)	9 (27.3%)
Strata 3: Transfusion="No" and serum erythropoietin level at least 200 mU/mL	0	0
Strata 4: Transfusion="Yes" and serum erythropoietin level at least 200 mU/mL	0	0
p-value[d]		<0.001
Subjects with erythroid response by IPSS risk category		
Low = 0[e]	2 (8.7%)	16 (45.7%)
Intermediate-1 = 0.5 to 1.0[e]	0	10 (20.4%)
Intermediate-2 = 1.5 to 2.0	0	0
High = ≥2.5	0	0
No IPSS at screening	0	1
p-value[d]		<0.001
Percentage of subjects with erythroid response at any time during the first 24 weeks of study for evaluable subjects[f]	2 (4.4%)	27 (32.9%)

[a] Erythroid response determined by the RRC according to the IWG 2006 criteria: Hemoglobin increase by ≥1.5 g/dL or relevant reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared with the pretreatment transfusion number in the previous 8 weeks; responses must last at least 8 weeks.

[b] p-value for treatment group differences are based on the Fisher exact test, 2-sided.

[c] The CMH p-value and percentages are based on the number of subjects in that strata: placebo, Strata 1 = 20 and Strata 2 = 19; epoetin alfa, Strata 1 = 38 and Strata 2 = 33.

[d] p-value for treatment group differences are based on the CMH test, 2-sided.

[e] The CMH p-value and percentages are based on the number of subjects in that IPSS category: placebo, Low 0 = 23 and Intermediate-1 = 22; epoetin alfa, Low 0 = 35 and Intermediate-1 = 49.

[f] The denominator excludes subjects who were determined by the RRC as not evaluable.

CMH = Cochran-Mantel-Haenszel; IPSS = International Prognostic Scoring Systems; IWG = International Working Group; RBC = red blood cell; RRC = Response Review Committee.

The results were similar in the PP analysis set, with 11 (34.4%) subjects in the epoetin alfa group who had an erythroid response compared with 0 subjects in the placebo group (p=0.002, using Fisher exact test, 2-sided). There was also a statistically significant difference between the treatment groups in the PP analysis set when the analysis was performed stratifying by either the stratification variables (Strata 1, 7 [63.6%] subjects; Strata 2, 4 [30.8%] subjects; p=0.001) or the IPSS risk categories (IPSS low, 7 [58.3%] subjects; IPSS intermediate-1, 4 [20.0%] subjects; p=0.001) at screening.

Individual subject assessment of erythroid response according to IWG 2006 criteria at Week 24 by the RRC is provided. Individual subjects identified by the RRC as early responding subjects and late responding subjects are provided.

Assessor's comment

As the primary efficacy endpoint, the percentage of the responders in the epoetin alfa group was significantly higher compared with the placebo group at any time during the first 24 weeks (31.8% vs. 4.4%; $p<0.001$). The response rates were in the same range than those mentioned in the methodology of the protocol (35% vs. 10%), though a bit lower than expected in the control group, allowing at least 80% power in the study.

This improved response rate in the epoetin alfa group compared with the placebo group was also confirmed in the per protocol population which showed that the major protocol deviations in the first 24 weeks of this study were not considered to have any clinically relevant impact on the primary efficacy endpoint.

Screening serum erythropoietin concentration of less than 500 mU/ml was required among the inclusion criteria. A difference in erythroid response rate was observed between subjects with baseline serum erythropoietin < 200 mU/mL and those ≥200 mU/mL (31.8% vs 0%). Thus, all of the responding subjects were in the strata with serum erythropoetin less than 200 mU/mL during screening. Therefore, it is recommended further in this procedure to analyze safety data regarding serum erythropoietin levels < or >200 mU/ml (see further discussion in the AR, **OM**).
In addition, others baseline factors had an impact on response of treatment: blood transfusion requirement (No=47.4% vs Yes=27.3%) and IPSS Risk Category (45.7% vs 20.4% between subjects with IPSS low-risk and those with intermediate-1-risk category).

The efficacy evaluation of epoietin alfa was focused in IPSS low-risk and intermediate-1-risk category. However, the MAH should also comment all the erythroid response according to the transfusions need (number of subjects receiving ≤2, >2 ou ≤4 RBC units in 8 weeks) in order to characterize the severity of the population and thus to better document the efficacy of epoietin alfa in MDS patients even if concerning a small size population (n=9) **(OC)**. Also, erythroid response was determined by the RRC according to the IWG 2006 criteria (ie *Hb increase by ≥ 1.5 g/dl or relevant reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared with the pretreatment transfusion number in the previous 8 weeks: responses must last at least 8 weeks*). Therefore, in order to further document these efficacy data, the MAH should separate the erythroid responses regarding to responses due to increase of Hb or due to decrease of transfusions **(OC)**.

Finally, individual subject assessment of erythroid response according to IWG 2006 criteria at Week 24 by the RRC was provided in the clinical study report. The percentages of the responders in the epoetin alfa group and in the placebo group were the same than in mITT analysis. Mean duration of response was longer in epoetin alfa group (27.5 weeks) than in placebo group (14 weeks). RRC also identified early responding subjects (those who responded according the IWG 2006 for 8 weeks up to Week 24 but not at Week 24) and late responding subjects (those who responded according the IWG 2006 at Week 24). 15.7 weeks of duration of response (n = 6) in early responding subjects and 10.6 weeks (n=2) in late responding subjects were observed. However, numbers of patients were too small to draw any conclusion.

III.4.2.1.2.7.2 Secondary Analysis

III.4.2.1.2.7.2.1 Erythroid Response

When comparing the frequencies of subjects with an erythroid response at Week 24 between treatment groups in the mITT analysis set using the Fisher exact test, 2-sided, the epoetin alfa group had statistically significantly more subjects who had an erythroid response than the placebo group based on both the RRC evaluation and the investigator evaluation, p<0.001 for both comparisons (Table 9).

Table 9: Erythroid Response at Week 24

(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
RRC: Subjects with erythroid response [a] at Week 24	1 (2.2%)	23 (27.1%)
p-value [b]		<0.001
CRF[c]: Subjects with erythroid response at Week 24	2 (4.4%)	31 (36.5%)
p-value [b]		<0.001

[a] Erythroid response determined by the RRC according to the IWG 2006 criteria: Hemoglobin increase by ≥1.5 g/dL or relevant reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared with the pretreatment transfusion number in the previous 8 weeks; responses must last at least 8 weeks. [b] p-value for treatment group differences are based on the Fisher exact test, 2-sided. [c] Investigator evaluation recorded in the CRF.

CRF = case report form; IWG = International Working Group; RBC = red blood cell; RRC = Response Review Committee.

In the PP analysis set, when comparing the frequencies of subjects with an erythroid response at Week 24 between groups using the Fisher exact test, 2-sided, the epoetin alfa group also had statistically significantly more subjects who had an erythroid response than the placebo group: 11 (34.4%) subjects compared with 0 subjects based on the RRC evaluation, p=0.002; and 15 (46.9%) subjects compared with 2 (9.5%) subjects based on the investigator evaluation, p=0.006.

Assessor's comment

The higher rate of erythroid response in epoetin alfa group than in placebo group was confirmed at Week 24 with both the RRC and investigator evaluation and in both ITTm and PP analysis evaluation. Nevertheless, there are discrepancies between investigators and RRC response evaluations. Disagreements should be detailed and discussed (number of responders versus non responders disagreements and if any, number of disagreements in positive response to treatment: ≥ 1.5 g/L versus < 4 units RBC transfusion) **(OC)**.

Ad hoc Re-Assessment of Response by Response Review Committee

During the RRC review (29 subjects), subjects were identified who had clinical benefit or even IWG 2006 response from study agent but did not initially meet the IWG 2006 criteria as applied in the study.

These included:

- Subjects who responded late in the study and did not meet the criteria for 8 weeks of response prior to Week 24 (ie, clinically notable increase in hemoglobin level, a reduction in the number of RBC transfusions, oscillations of hemoglobin values - especially those who responded only after an increase in the dose of epoetin alfa).
- Subjects for whom the baseline hemoglobin value was affected by pre-baseline RBC transfusion (information not available to RCC upon first review) and responded well to therapy. Baseline hemoglobin was re-calculated during the second review, which led to the identification of more subjects that demonstrated erythroid response.
- Subjects who had protocol-required dose stop or decrease due to "excessive" hemoglobin values (hemoglobin level >12g/dL or an increase by >2 g/dL) and were subsequently unable to reach and maintain the hemoglobin value for at least 8 weeks required for IWG 2006 response. These subjects were added to the identified IWG 2006 responders and the distribution of all subjects with observed clinical benefit from the therapy during the course of the study was analyzed in an ad-hoc analysis.
- Two subjects identified as responders by the RRC per IWG 2006 criteria in the first 24 weeks were inadvertently omitted from the analysis based on the initial review; these subjects were added to the analysis of the primary endpoint.

In summary, 29 subjects were re-reviewed by the RRC, 21 subjects were in the epoetin alfa group and 8 were in the placebo group. Of these 29 subjects, 12 were identified as responders in the epoetin alfa group; none were identified as responders in the placebo group. Two of the 12 subjects re-assessed as responders by the RRC were responders based on IWG 2006 criteria by Week 24 that were initially missing and subsequently included in the primary endpoint analysis, the remaining 10 responding subjects that could not be considered IWG 2006 responders due to some of the reasons listed above, were included only in the ad hoc analysis. In addition, during the initial RRC review, 2 subjects were identified who responded late in the study and demonstrated IWG 2006 response but not by Week 24, and therefore did not meet the primary endpoint criteria, but were considered responders in the ad-hoc analysis.

An ad hoc analysis was conducted to determine the distribution of all subjects who responded to study agent during their study participation (not limited by Week 24 time point as the primary endpoint) regardless of whether or not they met the IWG 2006 criteria. Therefore, the ad hoc analysis included all subjects considered IWG 2006 responders (27 in the epoetin alfa group and

2 in placebo group), responders to therapy who did not meet IWG 2006 criteria (10 in epoetin alfa group), and late responders (2 in the epoetin alfa group).

Based on the ad hoc analysis, a total of 39 of 85 (45.9%) subjects in the epoetin alfa group and 2 of 45 (4.4%) in the placebo group ($p<0.001$) were identified as responders to study agent regardless of whether or not they met the IWG 2006 criteria. All subjects re-assessed by the RRC as responders to study agent regardless of whether or not they met the IWG 2006 criteria were in the strata with serum erythropoietin <200 mU/mL, with higher rates among subjects who did not require transfusions in the 8 weeks prior to baseline and subjects who had low IPSS scores.

Assessor's comment

29 subjects were re-reviewed by the RRC: subjects identified who had clinical benefit: not limited by Week 24 time point as the primary endpoint regardless of whether or not they met the IWG 2006 criteria.

Of these 29 subjects, 12 were identified as responders in the epoetin alfa group in the ad-hoc analysis; none were identified as responders in the placebo group.

Finally, the ad-hoc analysis revealed a total of 39 of 85 (45.9%) subjects in the epoetin alfa group and 2 of 45 (4.4%) in the placebo group ($p<0.001$) identified as responders to study agent. All responders were in the strata with serum erythropoietin <200 mU/mL, with higher rates among subjects who did not require transfusions in the 8 weeks prior to baseline and subjects who had low IPSS scores.

The MAH mentioned that some factors could have contributed to a decrease of erythroid response in the EPOANE3021 study compared to clinical practice (see data of MDS registry studies further in the AR): 1/the dosing weight-based thus subjects were treated with a lower starting dose of epoetin alfa without dose change for the first 8 weeks, 2/the weekly Hb level monitor and strict dose adjustment requirements (hemoglobin concentration should not exceed 1 g/dL per 2 weeks, or 2 g/dL per month, or exceed 12 g/dL) which were approved in local product to minimize potential risk factors of TVEs and because of the limited data concerning the tumor progression in cancerous disease, 3/the major protocol deviations (e.g. deviations related to treatment dose).

However, the results obtained after the RRC re-assessment are similar than the investigator's report as described above confirming epoietin efficacy in erythroid response at Week 24.

III.4.2.1.2.7.2.2 Duration of Response

Based on the RRC assessment of subjects in the mITT analysis set who had an erythroid response at any time during the first 24 weeks, subjects in the epoetin alfa group had a mean (SD) response duration of 192.3 (88.92) days through completion of this 52-week study. In the placebo group, the mean (SD) response duration was 99.0 (69.30) days; however, this result is based only on 2 subjects and therefore statistical and clinical significance should not be made.

The results were similar for the PP analysis set, with subjects in the epoetin alfa group having a mean (SD) response duration of 209.1 (103.07) days; there were no subjects in the placebo group who had an erythroid response at any time during the first 24 weeks.

Assessor's comment

Based on the RRC assessment of responders set at any time during the first 24 weeks in the mITT analysis, subjects in the epoetin alfa group had a higher mean response duration of day than in the placebo group through completion of this 52-week study (192.3 ± 88.92 vs 99.0 ± 69.30 days). However, it was noted that no statistical analysis could be made due to the small size of placebo population and the high SD. Comparing to a published study (Park et al., 2008[8]) evaluating data from French and Belgian hematologic centers of the Groupe Francophone des Myelodysplasies (GFM) with 403 patients, median duration of response from the onset of rHuEPO was 24 months according to IWG 2006 criteria which is much higher than in this study. The MAH should discuss these observed discrepancies **(OC)**.

III.4.2.1.2.7.2.3 Responders at Week 48

Based on the RRC assessment of subjects in the mITT analysis set, there were 8 (9.4%) of 85 subjects in the epoetin alfa group who were responders at Week 48 (ie, had erythroid response at Week 24 and maintained the response through Week 48). In the PP analysis set, there were 4 (12.5%) of 32 subjects in the epoetin alfa group who were responders at Week 48. No subjects in the placebo group completed through Week 48.

According to protocol, subjects were to be discontinued during the treatment extension phase if they had no response after receiving the maximum epoetin alfa dose for at least 4 weeks. The number of subjects with a response to epoetin alfa at Week 48, as determined by the RRC, differs from the number of subjects who were allowed to continue in the study through Week 48 by the investigators. Twenty-nine (34.1%) subjects in the epoetin alfa group were allowed by the investigators to continue in the study up to Week 48 (Figure 2); for 4 of these subjects, this was a deviation from protocol.

[8] Park S et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008 Jan 15;111(2):574-82.

Assessor's comment

Based on the RRC assessment of subjects in the mITT analysis set, there were 8 (9.4%) of 85 subjects in the epoetin alfa group who were responders at Week 48 (ie, had erythroid response at Week 24 and maintained the response through Week 48). In the PP analysis set, there were 4 (12.5%) of 32 responders to epoetin alfa group. No subjects in the placebo group completed through Week 48.

Higher number of subjects (n = 29; 34.1%) in the epoetin alfa group was allowed by the investigators to continue in the study up to Week 48 (Figure 2); for 4 of these subjects, this was a deviation from protocol.

The RMS does agree that no conclusion could be drawn due to the small size of population.

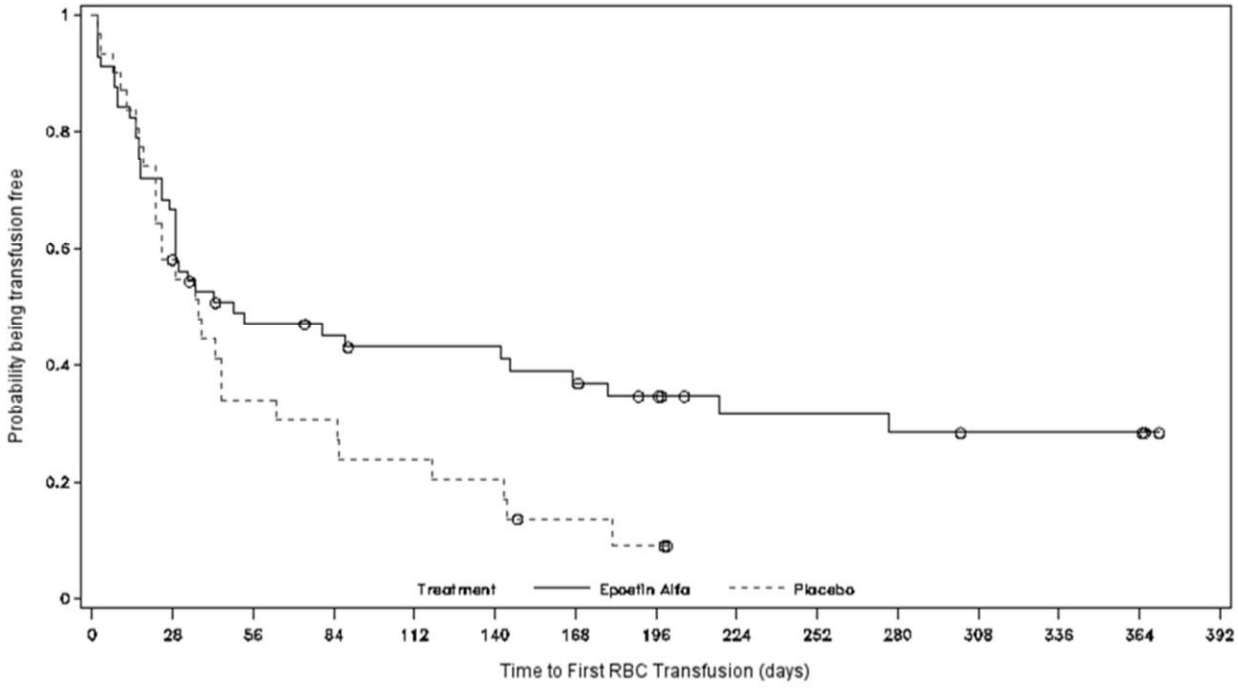
Approximately one third of the population continued the treatment up to Week 48, these supportive data confirmed efficacy data in this small population but should be interpreted regarding the safety data in order to avoid an overexposure of the drug **(OC)**.

III.4.2.1.2.7.2.4 Red Blood Cell Transfusions

III.4.2.1.2.7.2.4.1 Time to First Red Blood Cell Transfusion

The comparison of time to first RBC transfusion between the treatment groups was analyzed by the Kaplan-Meier analysis using the mITT analysis set. As shown in Figure 3, the epoetin alfa group begins to show separation from the placebo group at approximately Week 4 for the probability of being transfusion free, which is consistent with the mode of action of epoetin alfa.

Figure 3: Kaplan-Meier Plot of Time to First Red Blood Cell Transfusions
(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)



0 = Censored Observation

The log-rank test detected a statistically significant difference in time to first RBC transfusion in

The log-rank test detected a statistically significant difference in time to first RBC transfusion in the epoetin alfa group (median=49.0 days) compared with the placebo group (median=37.0 days) at p=0.046 (Table 10).

Table 10: Time to First RBC Transfusions
(Study EPOANE3021; Modified Intent-to-Treat Analysis Set)

	Placebo	Epoetin Alfa	p-value
Analysis set: modified intent-to-treat	45	85	
Number of subjects without any RBC transfusions	14	28	
Number of subjects in the analysis with at least 1 with RBC transfusion either in the 8 weeks prior to baseline and/or after randomization	31	57	
Number of censored observations (%)[a]	4 (12.9%)	19 (33.3%)	
Summary of time to first RBC transfusions (days)[b, c]			
N	31	57	
Maximum	200	371	
75% (95% CI)	86.0 (43.0, 181.0)	NE (167.0, NE)	
50% (95% CI)	37.0 (22.0, 64.0)	49.0 (29.0, 167.0)	
25% (95% CI)	18.0 (7.0, 24.0)	17.0 (9.0, 29.0)	
Minimum	2	2	
Mean (SE)	62.3 (11.17)	121.9 (15.93)	
95% CI	39.4, 85.1	90.0, 153.8	
Log-rank test			0.046
Hazard-Ratio (95% CI)[d]		1.653 (0.999, 2.736)	
Wald chi-square			0.051

a Percentage of censored observations is calculated from the number of subjects with at least 1 RBC transfusion either in the 8 weeks prior to baseline and/or after randomization.

b Kaplan-Meier Analysis.

c Time (days) to first RBC transfusion is from the baseline date to the date of first transfusion +1. Subjects without a transfusion had last date of contact as the censored date.

[d] Hazard ratio is the ratio of the hazard rates corresponding to the time to first RBC transfusion for the subjects in the placebo group versus the time to first RBC transfusion for the subjects in the epoetin alfa group.

CI = confidence interval; NE = not evaluable; RBC = red blood cell; SE = standard error.

In the PP analysis set, there was no statistically significant difference in time to first RBC transfusion between the epoetin alfa and placebo groups (medians: 29.0 and 24.0 days, respectively; p=0.321 using the log-rank test) or for the Hazard-Ratio (95% CI) (1.421 [0.701, 2.883]; p=0.330, Wald chi-square test).

Assessor's comment

The comparison of time to first RBC transfusion between the treatment groups was analyzed by the Kaplan-Meier analysis using the mITT analysis set. The epoetin alfa group begins to show separation from the placebo group at approximately Week 4 for the probability of being transfusion free.

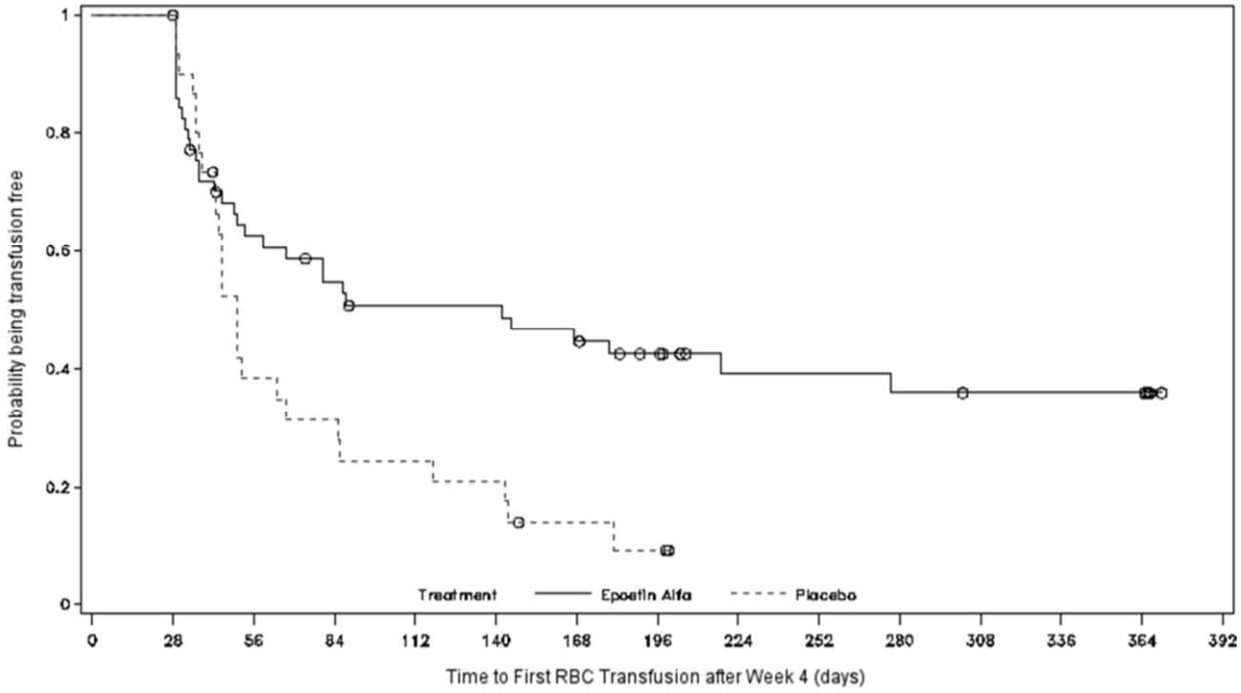
A weakly significant difference in time to first RBC transfusion in the epoetin alfa group compared with the placebo group was observed in ITTm analysis (median=49.0 vs. 37 days; p=0.046) but not in PP analysis (median=29.0 vs. 24 days; p=0.321).

III.4.2.1.2.7.2.4.2 Ad hoc Analyses of Time to First Red Blood Cell Transfusion

Time to First Red Blood Cell Transfusion After Week 4

The ad hoc comparison of time to first RBC transfusion after Week 4 between the treatment groups was analyzed by Kaplan-Meier analysis using the mITT analysis set. As shown in Figure 4, the epoetin alfa group begins to show separation from the placebo group before Week 8 for the probability of being transfusion free.

Figure 4: Kaplan-Meier Plot of Time to First Red Blood Cell Transfusions After Week 4
(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)



0 = Censored Observation

The log-rank test detected a statistically significant difference in time to first RBC transfusion after Week 4 in the epoetin alfa group (median=142.0 days) compared with the placebo group (median=50.0 days) at p=0.007. The Hazard-Ratio (95% CI) was 2.029 (1.194, 3.451) corresponding to the time to first RBC transfusion after Week 4 for the subjects in the placebo group versus the time to first RBC transfusion after Week 4 for the subjects in the epoetin alfa group with a p-value of 0.009 (Wald chi-square test).

Assessor's comment

The ad hoc comparison of time to first RBC transfusion after Week 4 between the treatment groups was analyzed by Kaplan-Meier analysis using the mITT analysis set. Higher statistically significant difference in time to first RBC transfusion after Week 4 in the epoetin alfa group compared with the placebo group (median= 142 vs. 50.0 days; p=0.007) has been observed with the HR of 2.029 (1.194, 3.451). Epoietin alfa had an impact on time to first RBC transfusion after 4 weeks of treatment, which is consistent with the mode of action of epoetin alfa.

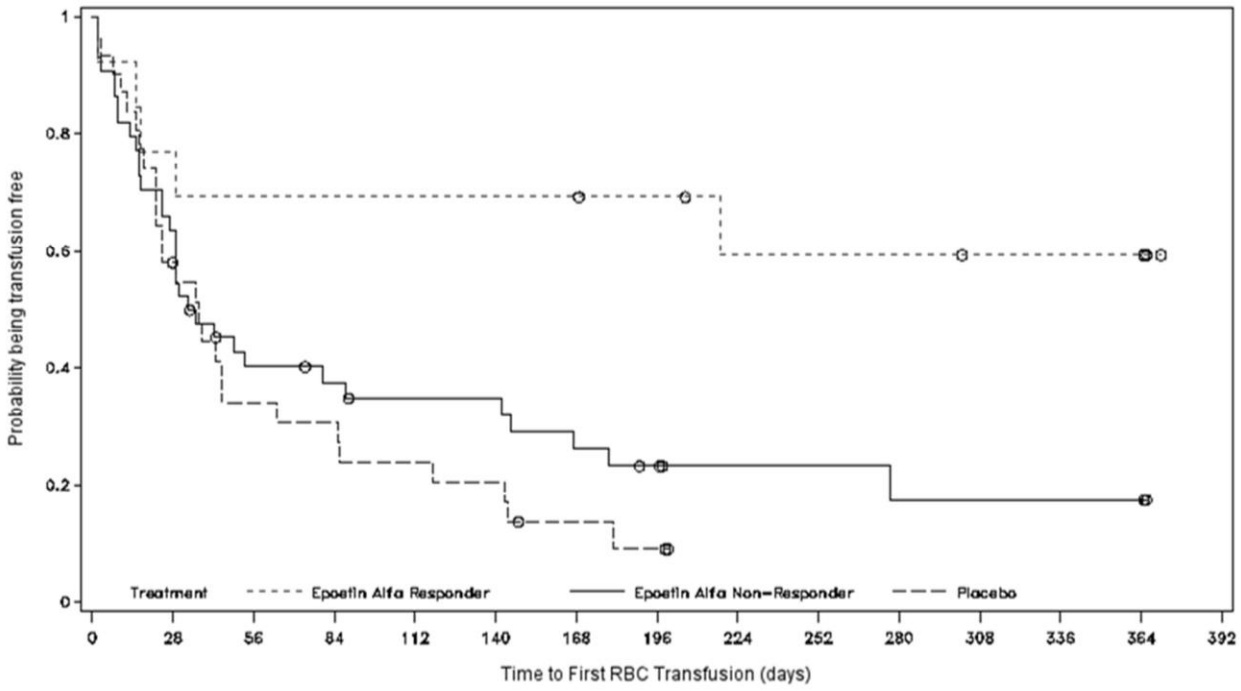
Time to First Red Blood Cell Transfusion by Response Review Committee Responder Status

The ad hoc comparison of time to first RBC transfusion by RRC responder status (ie, subjects who had a response to epoetin alfa compared with subjects who did not have a response to

epoetin alfa and all placebo subjects) between the treatment groups was analyzed by Kaplan-Meier analysis using the mITT analysis set. As shown in Figure 5, the subjects who had a response to epoetin alfa begin to show separation from subjects who did not have a response to epoetin alfa and all placebo subjects at approximately Week 4 for the probability of being transfusion free.

Figure 5: Kaplan-Meier Plot of Time to First Red Blood Cell Transfusions by Response Review Committee Responder Status

(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)



0 = Censored Observation

The log-rank test detected a statistically significant difference in time to first RBC transfusion between subjects who had a response to epoetin alfa (median [95% CI]=NE [not evaluable; 17.0, NE] days) and subjects who did not have a response to epoetin alfa (34.5 [24.0, 88.0] days) and all placebo subjects (37.0 [22.0, 64.0] days) at p=0.008. The Hazard-Ratio (95% CI) was 0.233 (0.087, 0.624) corresponding to the time to first RBC transfusion for all subjects in the placebo group versus the time to first RBC transfusion for subjects who had a response to epoetin alfa and 0.760 (0.454, 1.270) for all subjects in the placebo group versus subjects who did not have a response to epoetin alfa with a p-value of 0.015 (Wald chi-square test).

Assessor's comment

An ad hoc analysis was carried on the time to first RBC transfusion by RRC responder status (ie, subjects who had a response to epoetin alfa compared with subjects who did not have a response to epoetin alfa and all placebo subjects). The results were analyzed by Kaplan-Meier analysis using the mITT analysis set.

The subjects who had a response to epoetin alfa begin to show separation from subjects who did not have a response to epoetin alfa and all placebo subjects at approximately Week 4 for the probability of being transfusion free.

A statistically significant difference in time to first RBC transfusion between subjects who had a response to epoetin alfa (median [95% CI]=NE [not evaluable; 17.0, NE] days) and subjects who did not have a response to epoetin alfa (34.5 [24.0, 88.0] days) and all placebo subjects (37.0 [22.0, 64.0] days) at p=0.008.

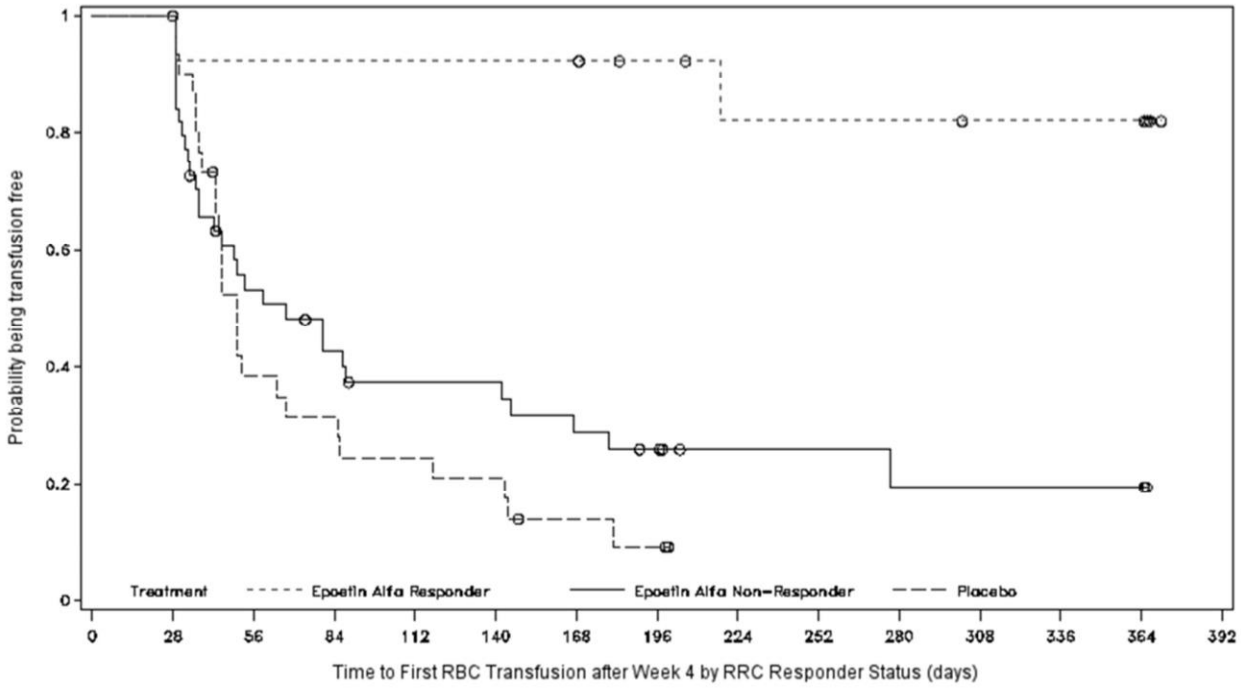
The HR was 0.233 (0.087, 0.624) corresponding to the time to first RBC transfusion for all subjects in the placebo group versus the time to first RBC transfusion for subjects who had a response to epoetin alfa.

However, a lesser difference was observed between subjects in the placebo group versus subjects who did not have a response to epoetin alfa (HR = 0.760 (0.454, 1.270) with a p-value of 0.015).

Time to First Red Blood Cell Transfusion After Week 4 by Response Review Committee Responder Status

The ad hoc comparison of time to first RBC transfusion after Week 4 by RRC responder status (ie, subjects who had a response to epoetin alfa compared with subjects who did not have a response to epoetin alfa and all placebo subjects) was analyzed by Kaplan-Meier analysis using the mITT analysis set. As shown in Figure 6, for the time to first RBC transfusion after Week 4 by RRC responder status, subjects who had a response to epoetin alfa show separation starting at Week 4 from subjects who did not have a response to epoetin alfa and all placebo subjects for the probability of being transfusion free.

Figure 6: Kaplan-Meier Plot of Time to First Red Blood Cell Transfusions After Week 4 by Response Review Committee Responder Status (Study EPOANE3021: Modified Intent-to-Treat Analysis Set)



0 = Censored Observation

The log-rank test detected a statistically significant difference in time to first RBC transfusion after Week 4 between subjects who had a response to epoetin alfa (median [95% CI]=NE [218.0, NE]) and subjects who did not have a response to epoetin alfa (67.0 [37.0, 142.0] days) and all placebo subjects (50.0 [43.0, 67.0] days) at $p<0.001$. The Hazard-Ratio (95% CI) was 0.071 (0.016, 0.309) corresponding to the time to first RBC transfusion after Week 4 for the subjects in the placebo group versus the time to first RBC transfusion after Week 4 for subjects who had a response to epoetin alfa and 0.706 (0.415, 1.200) for the subjects in the placebo group versus subjects who did not have a response to epoetin alfa with a p-value of 0.002 (Wald chi-square test).

Assessor's comment

The ad hoc analysis by the RRC confirmed a significant higher epoetin alfa effect after Week 4 between epoetin alfa responders versus non-responders (HR=0.706; [0.415, 1.200]) or placebo (HR=0.071; [0.016, 0.309]).

III.4.2.1.2.7.2.4.3 Transfusion-free Interval

Transfusion-free interval is defined as the time (days) from the last visit date minus baseline date plus 1 minus the number of days with transfusions (day on which 1 or more RBC or whole blood units were transfused). In the mITT analysis set, the mean (95% CI) number of transfusion-free days in the epoetin alfa group (212.4 [182.9, 241.9]) was numerically higher than in the placebo group (176.1 [156.9, 195.4]). The results were similar in the PP analysis set for the number of transfusion-free days (212.2 [164.6, 259.7] vs (172.6 [137.1, 208.1]).

Assessor's comment

In the mITT analysis set, the mean (95% CI) number of transfusion-free days in the epoetin alfa group (212.4 [182.9, 241.9]) was numerically higher than in the placebo group (176.1 [156.9, 195.4]). Results were similar in the PP analysis set.

III.4.2.1.2.7.2.4.4 Number of Red Blood Cell Units Transfused

For subjects in the mITT analysis set, similar percentages of subjects in the epoetin alfa and placebo groups received RBC transfusions in the 8 weeks prior to their baseline visit (51.8% and 48.9% of subjects, respectively). In the 8 weeks prior to baseline, 44 subjects in the epoetin alfa group received 75 transfusions (total RBC units=114; units per subject=2.6); and in the placebo group, 22 subjects received 36 transfusions (total RBC units=53; units per subject=2.4). A decrease in the percentage of subjects with transfusions over time through Week 24 was observed in the epoetin alfa group (ie, decrease from 51.8% in 8 weeks prior to baseline to 24.7% of subjects between Week 16 and Week 24); whereas, an increase was observed in the placebo group (ie, increase from 48.9% in 8 weeks prior to baseline to 54.1% of subjects between Week 16 and Week 24; Table 11). Between baseline and Week 24, 36 (42.4%) subjects in the epoetin alfa group received 163 transfusions (total RBC units=266; units per subject=7.4); and 26 (57.8%) subjects in the placebo group received 125 transfusions (total RBC units=196; units per subject=7.5). The mean (SD) transfusion-free interval for the first 24 weeks was 94.5 (54.65) days in the epoetin alfa group and 75.2 (42.90) days in the placebo group.

Table 11: Red Blood Cell Transfusions

(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
In 8 Weeks Prior to Baseline Visit N[a]		
	45	85
Number of subjects with transfusions (%)	22 (48.9%)	44 (51.8%)
Number of transfusions prior to baseline visit	36	75

Total units prior to baseline visit	53	114
RBC units required per subject receiving transfusions	2.4	2.6
Between Baseline and Week 8		
N[a]	45	85
Number of subjects with transfusions (%)	20 (44.4%)	31 (36.5%)
Number of transfusions between baseline visit and Week 8	39	61
Total units between baseline visit and Week 8	60	97
RBC units required per subject receiving transfusions	3	3.1
Between Week 8 and Week 16		
N[a]	41	82
Number of subjects with transfusions (%)	21 (51.2%)	23 (28.0%)
Number of transfusions between Week 8 and Week 16	41	60
Total units between Week 8 and Week 16	65	103
RBC units required per subject receiving transfusions	3.1	4.5
Between Week 16 and Week 24		
N[a]	37	77
Number of subjects with transfusions (%)	20 (54.1%)	19 (24.7%)
Number of transfusions between Week 16 and Week 24	45	42
Total units between Week 16 and Week 24	71	66
RBC units required per subject receiving transfusions	3.6	3.5
Between Baseline and Week 24		
N[a]	45	85
Number of subjects with transfusions (%)	26 (57.8%)	36 (42.4%)
Number of transfusions between baseline visit and Week 24	125	163
Total units between baseline visit and Week 24	196	266
RBC units required per subject receiving transfusions	7.5	7.4
Average transfusion-free intervals (days) for the first 24 weeks[b] N[a]		
	26	36
Mean (SD)	75.2 (42.90)	94.5 (54.65)
Median	54.3	54.5
Range	(41, 166)	(32, 166)

[a] N = number of subjects in the interval used to calculate the percentage of subjects with transfusions in the interval.

[b] Average transfusion-free days for the first 24 weeks per subject: Calculate the sum of the transfusion-free days within the first 24 weeks divided by the number of intervals within the first 24 weeks. RBC = red blood cell; SD = standard deviation.

The pattern observed for transfusion-free intervals in the first 24 weeks was similar to that observed in the mITT analysis set for the PP analysis set and for the subset of subjects in the mITT analysis set who had transfusions in the 8 weeks prior to baseline and/or during the first 24 weeks.

Assessor's comment

Similar percentages of subjects in the epoetin alfa and placebo groups received RBC transfusions in the 8 weeks prior to their baseline visit (51.8% and 48.9% of subjects, respectively).

In the 8 weeks prior to baseline, 44 subjects in the epoetin alfa group received 75 transfusions (units per subject=2.6); and in the placebo group, 22 subjects received 36 transfusions (units per subject=2.4) which is similar.

A decrease in the percentage of subjects with transfusions over time through Week 24 was observed in the epoetin alfa group (ie, decrease from 51.8% in 8 weeks prior to baseline to 24.7% of subjects between Week 16 and Week 24); whereas, an increase was observed in the placebo group (ie, increase from 48.9% in 8 weeks prior to baseline to 54.1% of subjects between Week 16 and Week 24).

Erythropoietin alfa is effective in term of decrease of transfusion. However, the MAH should detail the number of subjects receiving ≤2, >2 ou ≤4 RBC units in 8 weeks in order to better document the efficacy of epoietin alfa regarding the severity of the disease of these patients **(OC)**.

III.4.2.1.2.7.2.5 Hemoglobin and Reticulocytes Values Over Time

A statistically significant improvement was observed in mean hemoglobin levels over time in subjects in the epoetin alfa group from baseline (Day 1) through the first 24 weeks of the study compared with the placebo group ($p<0.001$ for all comparisons except Week 8, $p=0.001$). At Week 24, the mean increase from baseline in the hemoglobin levels in the epoetin alfa group was 1.04 g/dL and the mean decrease in the hemoglobin levels in the placebo group was -0.07 g/dL. The mean increase from baseline in the mean hemoglobin levels in the epoetin alfa group ranged from 1.13 to 1.63 g/dL after Week 24 through Week 48. Overall, for subjects in the PP analysis set, the mean hemoglobin values and trend over time from baseline through the first 24 weeks and after Week 24 through Week 48 were similar to that observed in the mITT analysis set.

A statistically significant ($p=0.038$) improvement was observed in mean reticulocyte counts in subjects in the epoetin alfa group at Week 24 compared with the placebo group. At Week 24, the mean increase from baseline in the reticulocyte counts in the epoetin alfa group was 24.86×10^9/L and the mean decrease in the reticulocyte counts in the placebo group was -4.24×10^9/L. The mean increase from baseline in the reticulocyte counts in the epoetin alfa group ranged from 25.76 to 56.08×10^9/L after Week 24 through Week 48. For subjects in the PP analysis set, the mean reticulocyte count at baseline was numerically higher in the placebo group than in the mITT analysis set (138.92×10^9/L vs. 92.67×10^9/L). There was no statistically significant difference in the PP analysis set between the treatment groups in the mean change in reticulocyte counts from baseline at Week 24 (19.85×10^9/L in the epoetin alfa group and -5.29×10^9/L in the placebo group; $p=0.249$). The mean increase from baseline in the reticulocyte counts in the epoetin alfa group ranged from -4.51 to 26.72×10^9/L after Week 24 through Week 48 in the PP analysis set.

Assessor's comment

An improvement of hemoglobin level has been observed at Week 24 in both mITT and per protocol analysis. Cautions should be taken after Week 24 because of the small size of population.
In addition, the efficacy analysis on patients stratified according to their baseline hemoglobin level was not performed as the study design allowed patients to receive blood transfusions prior to randomization/baseline, which made the baseline hemoglobin level susceptible to preceding blood transfusions.

In the ITT mean analysis, the low significance effect of erythropoietin alfa on mean reticulocyte could not be confirmed in the PP analysis due to the difference between the groups at the baseline.

III.4.2.1.2.7.2.6 Other Secondary Analyses

The Wilcoxon 2-sample test was used to evaluate differences between the treatment groups for the PRO(patient-reported outcome)/quality of life variables in the mITT and PP analysis sets for the FACT-An, EQ-5D and EQ VAS. No statistically significant difference in improvement was detected between the epoetin alfa group and the placebo group at any time point in either analysis set.

Previous studies have demonstrated that improvement in quality of life occurs in subjects who experienced an erythroid response.[13,22] Therefore, ad hoc analyses of the PRO/quality of life variables were performed to compare subjects who responded to epoetin alfa therapy with subjects who did not respond to epoetin alfa therapy and all placebo subjects:

- There was a statistically significant difference in improvement in the total FACT-An score for subjects who responded to epoetin alfa therapy compared with subjects who did not respond to epoetin alfa therapy in the mITT analysis set at Week 24 (p=0.025), but not at Week 48 (p=0.083; Table 12). There was no statistically significant difference in the total FACT-An score for subjects who responded to epoetin alfa therapy compared with all placebo subjects in the mITT analysis set at Week 24 (p=0.115).
- There was a statistically significant difference in improvement in the EQ-5D index score for subjects who responded to epoetin alfa therapy compared with subjects who did not respond to epoetin alfa therapy in the mITT analysis set at Week 24 (p=0.007), but not at Week 48 (p=0.075; Table 12). There was a statistically significant difference in improvement in the EQ-5D index score for subjects who responded to epoetin alfa therapy compared with all placebo subjects in the mITT analysis set at Week 24 (p=0.034).
- There was a statistically significant difference in improvement in the EQ VAS score for subjects who responded to epoetin alfa therapy compared with subjects who did not respond to epoetin alfa therapy in the mITT analysis set at Week 24 (p=0.037), but not at Week 48 (p=0.147; Table 12). There was no statistically significant difference in the EQ VAS score

for subjects who responded to epoetin alfa therapy compared with all placebo subjects in the mITT analysis set at Week 24 (p=0.282).

Assessor's comment

No statistically significant difference in improvement of quality of life was detected between the epoetin alfa group and the placebo group at any time point in either analysis set.

Therefore, ad hoc analyses of the PRO/quality of life variables were performed to compare subjects who responded to epoetin alfa therapy with subjects who did not respond to epoetin alfa therapy and all placebo subjects:

1. There was a statistically significant difference in improvement in either analysis set (FACT-An score, EQ-5D index, EQ VAS score) for subjects who responded to epoetin alfa therapy compared with subjects who did not respond to epoetin alfa therapy in the mITT analysis set at Week 24, but not at Week 48.

2. No statistically significant difference in the total FACT-An score and the EG VAS score for subjects who responded to epoetin alfa therapy compared with all placebo subjects in the mITT analysis set at Week 24.

3. There was a weakly statistically significant difference (p=0.034) in improvement in the EQ-5D index score for subjects who responded to epoetin alfa therapy compared with all placebo subjects in the mITT analysis set at Week 24.

Thus, improvement of epoietin alfa in quality of life was observed mostly in epoetin alfa responders at Week 24. A Phase 3, prospective randomized trial in lower-risk MDS subjects had also demonstrated that improvements in QoL was limited to those subjects with an erythroid response upon treatment[9].

[9] Greenberg PL et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood. 2009; 114, (12): 2393-2400.

Table 12: Summary of Change From Baseline at Week 24 and Week 48 for Total FACT-An, EQ-5D Index, and EQ VAS Scores
(Study EPOANE3021: Modified Intent-to-Treat Analysis Set)

	Epoetin Alfa Responders		Epoetin Alfa Non-Responders		Placebo	
	Observed[a]	Change from Baseline[a]	Observed[a]	Change from Baseline[a]	Observed[a]	Change from Baseline[a]
Total FACT-An score						
Week 24						
N	26	26	40	40	34	34
Mean (SD)	139.775 (30.6664)	8.090 (18.1614)	116.537 (36.1048)	-6.292 (26.7063)	132.702 (25.9611)	0.018 (18.0910)
Median	149.250	3.600	120.915	-4.175	132.580	-0.840
Range	(79.83, 180.00)	(-21.34, 51.73)	(36.00, 184.00)	(-85.00, 51.00)	(82.67, 176.00)	(-31.00, 34.83)
(Lower 95% CI, upper 95% CI for the mean)	(127.389, 152.162)	(0.754, 15.426)	(104.990, 128.083)	(-14.833, 2.249)	(123.644, 141.760)	(-6.294, 6.330)
p-value[b]		0.064		0.153		0.749
p-value[c]				0.025		0.115
Week 48						
N	21	21	8	8	-	-
Mean (SD)	145.180 (28.5203)	11.052 (18.2270)	138.301 (26.0372)	-2.480 (15.3148)	-	-
Median	150.830	8.000	141.835	-2.300	-	-
Range	(75.33, 178.79)	(-22.17, 53.00)	(100.00, 174.83)	(-28.09, 20.00)	-	-
(Lower 95% CI, upper 95% CI for the mean)	(132.198, 158.162)	(2.755, 19.349)	(116.534, 160.069)	(-15.284, 10.324)	-	-
p-value[b]		0.014		0.641		-
p-value[c]				0.083		-
EQ-5D Index Score						
Week 24						
N	25	25	41	41	34	34
Mean (SD)	0.800 (0.1738)	0.103 (0.2204)	0.606 (0.3407)	0.098 (0.3406)	0.705 (0.2464)	0.042 (0.2779)
Median	0.810	0.040	0.690	0.000	0.730	0.000
Range	(0.31, 1.00)	(-0.31, 0.56)	(-0.24, 1.00)	(-1.18, 0.53)	(0.06, 1.00)	(-0.74, 0.60)
(Lower 95% CI, upper 95% CI for the mean)	(0.728, 0.871)	(0.012, 0.194)	(0.498, 0.713)	(-0.205, 0.010)	(0.619, 0.791)	(-0.139, 0.055)
p-value[b]		0.058		0.076		0.385
p-value[c]				0.007		0.034
Week 48						
N	21	21	8	8	-	-
Mean (SD)	0.765 (0.2996)	0.071 (0.1484)	0.728 (0.2650)	0.071 (0.1738)	-	-

Median	0.800	0.000	0.690	0.000	-	-
Range	(-0.02, 1.00)	(-0.15, 0.44)	(0.26, 1.00)	(-0.34, 0.20)	-	-
(Lower 95% CI, upper 95% CI for the mean)	(0.629, 0.902)	(0.004, 0.139)	(0.506, 0.949)	(-0.217, 0.074)	-	-
p-value[b]		0.036		0.375		-
p-value[c]				0.075		-
EQ Visual Analog Scale[d]						
Week 24						
N	24	24	37	37	34	34
Mean (SD)	67.9 (21.26)	10.1 (19.64)	57.8 (21.70)	-2.8 (20.62)	65.7 (21.17)	4.8 (23.19)
Median	66.0	9.5	60.0	0.0	67.5	2.5
Range	(30, 100)	(-15, 72)	(10, 100)	(-65, 30)	(6, 100)	(-30, 95)
(Lower 95% CI, upper 95% CI for the mean)	(58.9, 76.9)	(1.8, 18.4)	(50.6, 65.1)	(-9.7, 4.1)	(58.3, 73.1)	(-3.3, 12.9)
p-value[b]		0.022		0.562		0.357
p-value[c]				0.037		0.282
Week 48						
N	20	20	7	7	-	-
Mean (SD)	72.5 (19.21)	13.4 (19.28)	68.3 (24.64)	-0.3 (16.55)	-	-
Median	77.5	10.0	70.0	0.0	-	-
Range	(40, 100)	(-10, 72)	(28, 100)	(-30, 20)	-	-
(Lower 95% CI, upper 95% CI for the mean)	(63.5, 81.5)	(4.3, 22.4)	(45.5, 91.1)	(-15.6, 15.0)	-	-
p-value[b]		0.001		>0.999		-
p-value[c]				0.147		-

[a] For postbaseline visits, only subjects with a baseline and at least 1 postbaseline visit are included in the statistics.

[b] The change from baseline score at each visit and at endpoint has been tested using the Wilcoxon signed rank test.

[c] Between-group comparisons of the change from baseline score has been tested by means of the Wilcoxon 2-sample test.

[d] Scale 0 = "Worst imaginable health state" and 100 = "Best imaginable health state".

CI = confidence interval; EQ-5D = EuroQol 5-dimension questionnaire; EQ VAS = EuroQol visual analog scale; FACT-An = Functional Assessment of Cancer Therapy Anemia/Fatigue; SD = standard deviation.

III.4.2.2 Supportive studies

III.4.2.2.1 Methods

These studies were conducted and reported by the investigators in France, Italy and Spain, to assess long-term safety and efficacy in the real-world clinical use of epoetin alfa (or ESAs) in patients with low- or intermediate-1-risk MDS.

The French MDS Registry (GFM） analyzed data collected in the Registry from 2003 to 2014. The objective of the study was to assess EPREX use and to characterize its effectiveness and tolerance in patients with low or intermediate-1-risk MDS (including those previously treated with ESAs and other agents, or patients with secondary MDS [15%]). 3,637 patients have been included in this study. Among them, 2,300 (70%) patients had low- or intermediate-1-risk MDS and 1,380 (60%) patients had initially a hemoglobin level <10g/dL. The data collected in this registry included age, sex and the geographic location of the patients, the primary or secondary nature of MDS, the time of diagnosis, the hematologic characteristics especially hemoglobin level before any transfusion and the result of bone marrow smear, the karyotype, the IPSS and IPSS-R scores, the treatment and the efficacy result, failure and the time to response, the next treatments and the MDS evolution.

A total of 142 patients were treated with EPREX for anemia (117 patients received EPREX as first intention and 25 patients received it as second line).

The report also included the overall survival data from a total of 253 patients treated with ESA (erythropoiesis-stimulating agents including EPO and DAR), including 120 patients resistant to ESA (with or without granulocyte colony-stimulating factor [G-CSF]), 66 patients with erythroid relapse not explained by a concomitant increase in bone marrow blasts, and 67 who responded and had not relapsed at last follow-up or death.

>70% (100 of 142) of subjects who received EPREX had 40,000 IU as the initial dose.

The Italian MDS Registry (FISM) included a total of 2,487 patients with MDS and 1,411 patients with low- or intermediate-1-risk MDS for the period of 1999 to 2013.

The objectives of the study were: (1) to evaluate the overall survival in patients with or without EPO treatment; (2) to evaluate the progression to AML; (3) to compare the overall survival in EPO-responders vs non-responders (according IWG 2006 erythroid response criteria); (4) to evaluate the response duration for responders. There was a follow-up period of 52 weeks in this study. In addition, data in this study were further analyzed according to patients' baseline hemoglobin level (>10 g/dL, <10 g/dL [8 to 10 g/dL, and <8 g/dL]).

The data collected in this registry included personal data, eg, age, sex, death, medical history, diagnosis (MDS diagnosis, FAB/WHO classification, IPSS/ WHO classification–based Prognostic Scoring System (WPSS)/IPSS-R risk scores, transfusion history, complete blood test), treatment details (type, dosage and schedule, time, response, response duration), and treatment and the efficacy result, ie, survival, transfusion needs, and changing MDS subtype classification.

Among the 1,411 patients, 1,049 patients were included in the analysis, 335 patients were treated with EPO and 714 patients did not receive any ESAs.

All patients (335) who received EPO alpha had a dosage ranging between 40,000 and 80,000 U/week.

The Spanish MDS Registry (RESMD, Spanish Registry of Myelodysplastic Syndromes) managed by GESMD (Spanish Group of Myelodysplastic Syndromes) was opened in 1979, and included a total of 959 patients diagnosed with low- or intermediate-1-risk MDS until 31 December, 2011.

The primary objective of the Spanish MDS registry study was "to retrospectively collect and evaluate the Spanish experience with the treatment of anemia in patients with a diagnosis of lower-risk MDS according to IPSS, evaluating the efficacy and safety of ESA treatment administered for at least 24 weeks".

The study SPRESAS (SPanish Registry of Erythropoietic Stimulating Agents Study) was conducted on "ESAs" users, and included 722 patients diagnosed with low- or intermediate-1-risk MDS who had evaluable data. Among them, 530 patients received treatment with ESAs (including 24 patients received EPREX) and 192 patients received blood transfusion support (Supp arm). The data collected in this registry included age, sex, baseline status, follow-up, comorbidities, MDS disease diagnosis (WHO2008 classification), hematologic characteristics, transfusion dependency, IPSS and IPSS-R scores, and efficacy and safety results, ie, MDS disease progression. The study included adult subjects with diagnosis of MDS according to WHO or FAB classifications of low risk FAB (IPSS low- or intermediate-1-risk) with anemia (hemoglobin [Hb] ≤11 g/dL) and treatment (ESA/support) started before December 31, 2011.

Most patients who received epoetin had a dose range between 30,000 and 40,000 IU/week.

III.4.2.2.2 Results

III.4.2.2.2.1 Demographic and Baseline Characteristics in registry studies

Table 13: Overview of Demographics and Baseline Characteristics in Population Studied in EPOANE3021 and MDS Registry Studies

Category	EPOANE3021			French MDS Registry	Italian MDS Registry			Spanish MDS Registry	
	Placebo	Epoetin Alfa	Total		EPO	Non-EPO	Total	ESA	Support
Baseline Hemoglobin level (g/dL)									
N	45	85		142 (EPREX)	335	714	1049	530	192
Mean (SD)	9.2 (0.85)	9.1 (0.94)			----------[<8 g/dL]----------				
Median	9.4	9.3		8.9	38 (11%)	82 (11%)	120 (11%)	10.0	9.0
Range	(6.9,10.5)	(6.8, 11.0)		(5.7, 10.0)	----------[8-10 g/dL]----------				
					205 (61%)	243 (34%)	448 (43%)		
					----------[>10 g/dL]----------				
					92 (28%)	389 (55%)	481 (46%)		
Baseline Serum EPO level (mU/mL)									
N	45	85	130	142 (EPREX)				342	36
Median				99				59.5	142.5
Range				(6, 1509)					
<200 mU/mL	39 (86.7%)	71 (83.5%)	110(84.6%)						
≥200 mU/mL	6 (13.3%)	13 (15.3%)			19 (14.6%)				
RBC Transfusion[a]									
N	45	85	130	142 (EPREX)	335	714	1049	329	192
Transfusion (yes)	22 (48.9%)	44 (51.8%)	66 (50.8%)		38 (11%)[b]	82 (11%)[b]	120 (11%)[b]	185(56.2%)	184(95.8%)
Transfusion (no)	23 (51.1%)	41 (48.2%)	64 (49.2%)		297 (89%)[c]	632 (89%)[c]	929 (89%)[c]	144(43.8%)	8 (4.2%)
Age (years)									
N	45	85	130	142 (EPREX)	335	714	1049	530	192
Mean (SD)	74.1 (9.25)	74.3 (8.62)	74.2 (8.81)		75	71	72		

Median	75.0	75.0	75.0	75				77	76
Range	(36, 87)	(40, 94)	(36, 94)						
Sex									
N	45	85	130	142 (EPREX)	335	714	1049	530	192
Male	25 (55.6%)	46 (54.1%)	71 (54.6%)		185(55%)	430(60%)	615(59%)	280(54%)	111(58%)
Female	20 (44.4%)	39 (45.9%)	59 (45.4%)	50%	150(45%)	284(40%)	434(41%)	240(46%)	81(42%)

EPO=erythropoietin; ESA=erythropoiesis stimulating agent; MDS=myelodysplastic syndromes; RBC=red blood cell; SD=standard deviation.

[a] : RBC transfusion: In the EPOANE3021 study, subjects who received RBC transfusion within 8 weeks prior to baseline visit will be considered as "yes". RBC transfusion-dependence or independence definitions may vary by MDS registry studies.

[b] : Hemoglobin level <8 g/dL;

[c] : Hemoglobin level ≥8 g/dL

Table 14: Overview of MDS Classification in Population Studied in EPOANE3021 and MDS Registry Studies

Category	**EPOANE3021**			**French MDS Registry**	**Italian MDS Registry**			**Spanish MDS Registry**	
	Placebo	Epoetin Alfa	Total		EPO	Non-EPO	Total	ESA	Support
WHO Classification									
N	44	82	126	142 (EPREX)	335	714	1049	530	192
RA	11 (24.4%)	7 (8.2%)	18 (13.8%)	25	113(34%)	183(26%)	296(28%)		
RARS	2 (4.4%)	9 (10.6%)	11 (8.5%)	30	44(13%)	50(7%)	94(9%)	101(19.1%)	14 (7.3%)
RCDU								48 (9.1%)	13 (6.8%)
RCMD	21 (46.7%)	36 (42.4%)	57 (43.8%)	48	125(37%)	222(30%)	347(33%)	182(34.5%)	42 (21.9%)
RCMD-RS	5 (11.1%)	12 (14.1%)	17 (13.1%)						
RAEB-1	1 (2.2%)	10 (11.8%)	11 (8.5%)	21	36(11%)	131(18%)	167(16%)	18 (3.4%)	19 (9.9%)

RAEB-2	0	1 (1.2%)	1 (0.8%)		3(1%)	18(3%)	21(3%)	2 (0.4%)	11 (5.7%)
MDS-U	0	1 (1.2%)	1 (0.8%)	5	3(1%)	75(11%)	78(7%)	3 (0.6%)	0
5q-	3 (6.7%)	2 (2.4%)	5 (3.8%)	5	11(3%)	35(5%)	46(4%)	17 (3.2%)	10 (5.2%)
AML	0	0	0						
CMML								33 (6.3%)	10 (5.2%)
CMML1				5					
CMML2				1					
MDS/CMPN								7 (1.3%)	2 (1%)
Not Available	1 (2.2%)	4 (4.7%)	5 (3.8%)	2 (ICUS)				117(22.2%)	71 (37%)
IPSS Score									
N	45	85	130	142 (EPREX)	335	714	1049	484	185
Low=0	23 (51.1%)	35 (41.2%)	58 (44.6%)	77	208(62%)	367(51%)	575(55%)	305(63%)	74 (40%)
Intermediate 1=0.5 to 1.0	22 (48.9%)	49 (57.6%)	71 (54.6%)	45	127(38%)	347(49%)	474(45%)	179 (37%)	111(60%)
Intermediate 2=1.5 to 2.0	0	0	0						
High = ≥2.5	0	0	0						
Missing	0	1 (1.2%)	1 (0.8%)	20 (unknown karyotype)					

5q- = myelodysplastic syndromes associated with isolated del(5q); AML = acute myeloid leukemia; CMML = chronic myelomonocytic leukemia; CMPN = chronic myeloproliferative neoplasies; EPO=erythropoietin; ESA=erythropoiesis stimulating agent; IPSS=International Prognostic Scoring System; MDS=myelodysplastic syndromes; MDS-U = myelodysplastic syndrome, unclassified; RA = refractory anemia; RARS = refractory anemia with ringed sideroblasts; RAEB = refractory anemia with excess blasts; RCDU = refractory cytopenia with unilineage dysplasia; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts; WHO=World Health Organization.

III.4.2.2.2.2 Efficacy Results

III.4.2.2.2.2.1 Erythroïde Response

French MDS Registry Study

Erythroïde response in the French study was stratified by the line of treatment.

In patients having received Eprex as first treatment (n=117)
In 117 patients who received Eprex as first line of treatment, the overall response rate was 58%. 94% of the patients responded in 8 weeks (4-12 weeks). The median duration of response was 25 months (1-108 months). The median duration of treatment in patients who did not respond (42%) was 9 months (1-53 months).
Seven patients stopped the treatment for secondary effects (see section 4.3.3.2).

In patients having received Eprex in second line (n=25)
In patients who received Eprex for second line of treatment, the treatment before introduction of Eprex was another ESA (23 cases), Revlimid (1 case) and Danatrol (1 case).

5 patients changed ESA for unknown reason; the switch to Eprex induced a response rate in 4 of them.

Among the subpopulation who responded to previous ESA one change was related to intolerance and substitution by Eprex induced the same intolerance.

For the 23 patients treated by another ESA (74% by Darbepoetine (17 patients) and 26% EPOα (6 patients)), the response rate was 70% (16 responders) and 7 of them were non-responders.

In this subpopulation, Eprex induced a response rate in 4 patients (57%). The median response duration was 20 months (3-45 months).

For the 10 patients who were responders to ESA and then failed, the switch to Eprex induced 4 responses during 7 months (4-10 months).

Italian MDS Registry Study

In this study erythroid response was based on IWG2006 criteria, and analyzed according to the patients' baseline Hb level:

In patients patients with Hb level >10 g/dL (n=481)
92 (19%) patients were treated with EPOα and 87 patients evaluable for response, the erythroid response rate was 63%.

In patients patients with Hb level ≤10 g/dL (n=568)
243 (42%) patients were treated with EPOα and 224 patients evaluable for response, the erythroid response rate was 61%. Median duration of response was 82 weeks.

In 448 patients non-transfused with Hb level 8 to 10 g/dL, the erythroid response rate was 69%.

In 120 patients transfused with Hb level <8 g/dL, the erythroid response rate was 14%.

The report indicated that the response rate to EPOα was significantly higher in non-transfused subgroup over the transfused patients: 69% versus 14%, respectively (p<0.001).

Spanish MDS Registry Study
In this study erythroid response was based on IWG2006 criteria.

In 530 patients, 310 (58.5%) of these patients had achieved erythroid response. However, among these 530 patients, 243 received Aranesp (darbepoetin alfa), 24 received Eprex, 75 received epoetin beta, 15 received other epoietins (theta, Z, etc, ..) and in 173 patients the type of ESA was not available. In the 24 patients received Eprex, 15 (62.5% patients achieved erythroid response).

The median duration of response was 653 days (21.7 months). The responses obtained with various ESAs used were similar among the groups analyzed.

Among the factors influencing response to ESA treatment included in the analyses, the following have shown to play an important role in the univariate analysis: baseline transfusion dependency (No vs Yes: p=0.033), baseline hemoglobin level (<10 vs ≥ 10 g/dL: p=0.032), percentage of blasts in PB (p=0.045) and BM (p=0.022), ferritin levels (p=0.034), IPPS cytogenic category (p=0.005) and EPO levels.

However, in the multivariate analysis, the only factor that retained statistical significance was endogenous EPO levels (< vs ≥ 200 mU/mL: p=0.036 in multivariable analysis).

III.4.2.2.2.2.2 Overall survival

French MDS Registry Study

In all population treated by Eprex (142 patients), 67 patients were still responders with a median follow-up of 76.7 months from the onset of ESA. By definition, none had progressed to AML.

35 patients died.

In these patients, median survival from the onset of ESA was 65.8 months (95% CI: 47.9–not reached) compared with 40.1 months (95% CI: 31–53.4) in patients with early ESA failure (who lost response within 6 months) and 90.7 months (95% CI: 68.9–not reached) in patients with later failure (lost response after ≥6 months). The difference was statistically significant between the patients with no failure (who did not lose response) and early failure (p=0.01) but not with those with late failure (P=0.09).

Italian MDS Registry Study

In the Italian MDS registry study, overall survival was analyzed using standard survival analysis methods, including Kaplan-Meier product-limit survival curve estimates and log-rank tests.

Overall survival was defined as the time from diagnosis to death from any cause. Concerning overall survival of the whole group of patients, no significant improvement in OS of EPO treated patients could be demonstrated. However, EPO treated patients were a more unfavorable subgroup in comparaison to EPO non-treated patients in terms of Hb baseline values. A total of 481 patients with Hb level >10 g/dL showed no improvement, 568 patients with Hb level ≤10 g/dL showed an improvement, and patients with only un-transfused mild anemia and a baseline Hb level ranging from 8 to 10 showed a significant improvement in overall survival with a median overall survival of 64 months in patients treated with EPO vs. 43 months in patients without EPO treatment. Patients dependent on transfusion with a baseline level of Hb less than 8 g/dL failed to achieve an improvement in overall survival probably due to the biological suppression of erythroid cells production in bone marrow typical of transfused patients as suggested by the authors.

Spanish MDS Registry Study

In the Spanish MDS registry study, overall survival was defined as the time between introduction of EPO treatment (or diagnosis in the transfusion support arm) and death. Overall survival was analyzed using univariate and multivariate Cox proportional hazards regression.

The analysis for overall survival between patients who received ESA and those who received transfusion support showed a statistically significant improvement in the overall survival in

patients receiving ESA. The median overall survival was 6.7 and 3.1 years, for the ESAs and the transfusion support group, respectively ($p<0.0001$).

Assessor's comment

1. Erythroid Response

It was mentioned by the MAH that the erythroid response rate in the EPOANE3021 study showed a statistically significant difference between the epoetin alfa group and the placebo groups; however, the "absolute" value was lower than those reported in the MDS registry studies (31.8% vs. an average of 61%). These results must be interpreted with cautions, as registries were observational in nature. There was no control arm in the French registry and the data concerning erythroid response in the transfusion support group from the Spanish registry were not mentioned in their report. Registries should be considered as supporting studies with descriptive data.

The different national registers showed some heterogeneities concerning:
- Hb level at the baseline: <10g / dL for the French registry, stratified ≤ or > 10 g/dl for Italian registry, <11g / dL for the Spanish registry,
- Distribution of different stage of disease,
- Number of EPO alfa treated patients:

The French registry included 142 patients including 117 in first-line therapy. Only these patients can be analyzed.

The Italian registry included 92 patients treated with alfa EPO with Hb level >10g/dl which 87 were evaluable for response. 243 patients treated with alfa EPO with Hb level ≤ 10g/dl which 224 were evaluable for response.

The Spanish register included only 24 patients treated with alfa EPO.

However, all patient inclusion is justified regarding the pathology and stage of disease.

The Italian register provided the most significant results, with data on survival.

The following baseline factors influencing erythroid response are observed in the registries:

The French study categorized patients as "early failures" (including resistance and relapse after < 6 months of response), or "later failure" (that is, relapse after ≥ 6 months). These descriptive results allowed to more document the overall survival (Kelaidi et al. 2013).

Detailed results of the 5-year cumulative incidence of AML and median OS after failure were published (Kelaidi et al. 2013). Incidence of AML and median OS after failure in early and later failure were 21.6% and 9% (p=0.02) and 36.7 (3.1) and 54.3 months (4.5 years) (P=0.02),

respectively. Early failure to ESA and a baseline diagnosis of refractory anemia with excess blasts (RAEB)-1 were prognostic factors for AML progression and, along with trisomy 8, for shorter OS. Median OS from treatment onset was 40, 90.7 and 65.8 months in early failure, later failure and no relapse, respectively (p=0.001). Thus, the authors concluded that lower-risk MDS with early failure to ESA have a relatively unfavorable outcome, and should be offered alternative treatments.

In the Spanish MDS registry study, overall survival was defined as the time between introduction of EPO treatment (or diagnosis in the transfusion support arm) and death. Overall survival was analyzed using univariate and multivariate Cox proportional hazards regression.
The analysis for overall survival between patients who received ESA and those who received transfusion support showed a statistically significant improvement in the overall survival in patients receiving ESA. The median overall survival was 6.7 and 3.1 years, for the ESAs and the transfusion support group, respectively (p<0.0001).

In the Italian registry, in the group of the 92 patients with Hb level higher than 10 g/dL in which EPO treatment is not usually suggested by international clinical guidelines, the EPO response rate was as high as 63% but this did not induced an improvement in OS (defined as the time from diagnosis to death from any cause). The authors concluded that in EPO treated-patients with Hb level higher than 10 gr/dL, which is not suggested by international guidelines, seems not to improve survival and cannot be encouraged according to our results.
Finally the group of the 224 patients with Hb level lower than 10 g/dL in which EPO treatment is suggested by international clinical guidelines the global response rate was 61% and an improvement in OS was evident but the difference between EPO and not EPO treated patients did not reached the significance level. The difference in OS is in any case evident between EPO responders and EPO non-responders or non-treated patients.
Finally it was concluded by the authors that only untransfused mild anemic patients with baseline Hb level ranging from 8 to 10 (response rate of 69%) showed significant survival improvement in treated patients as compared to non-treated ones. At the opposite transfusion dependent patients with a baseline level of Hb less than 8 g/dL failed to achieve an improvement in OS.

III.4.3 Clinical safety

The safety data from the following studies and sources are included:

- One Phase 3 efficacy and safety study EPOANE3021: a randomized, double-blind, placebo-controlled, multicenter study evaluating epoetin alfa (EPREX) versus placebo in anemic patients with IPSS low- or intermediate-1-risk myelodysplastic syndromes.
- One supportive Phase 3 efficacy and safety study EPO-ANE-3018: a randomized, doubleblind, placebo-controlled, multicenter study evaluating epoetin alfa (Procrit) initiated

at 40,000 IU every week or 80,000 IU every week versus placebo in subjects with IPSS low or intermediate-1-risk myelodysplastic syndromes at risk for transfusion.

- Three supportive MDS registry studies: French MDS registry study (EPREX, the GFM Experience); Italian Registry study (FISM), and Spanish Registry study (SPRESAS).

III.4.3.1 Main study: EPOANE3021

III.4.3.1.1 Patient exposure

A total of 130 subjects (85 in the epoetin alfa group and 45 in the placebo group) were included in the safety analysis. The safety analysis set included all subjects who were randomly assigned to a treatment group and received at least 1 dose of study agent (ie, epoetin alfa or placebo). The safety analysis set is the same for the first 24-week period and the entire study period.

Subjects received a starting dose of 450 IU/kg (first 8 weeks) adjusted to a maximum of 1,050 IU/kg (after Week 8) administered subcutaneously once every week. The maximum total dose was 40,000 IU administered once every week during the first 8 weeks of treatment, and 80,000 IU once every week after Week 8. The actual median weekly dose was 730.4 IU/kg in the epoetin alfa group and 850.0 IU/kg in the placebo group.

The primary focus of the safety analysis was based on treatment-emergent adverse events and other safety data through the first 24 weeks of the study where the comparison of the 2 groups can be performed. At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase. Safety data for the treatment extension phase only (ie, after Week 24 through end of study) were not summarized separately. Instead, the results for the entire study are presented and include all data from baseline through Week 52 (ie, end-of-study visit after end of treatment extension phase Week 48). For subjects who did not enter the treatment extension phase, an end of study visit that included safety evaluations was performed at Week 28 (ie, 4 weeks after last dose at Week 24); all data after Week 24 through Week 28 for these subjects are included in the entire study period data set.

Assessor's comment

The 85 subjects of the epoetin alfa group and 45 subjects of the placebo group were included in the safety analysis. The safety analysis set included all subjects who received at least 1 dose of study agent.

Subjects received a starting dose of 450 IU/kg adjusted to a maximum of 1,050 IU/kg once every week. The maximum total dose was 40,000 IU administered once every week (the first 8 weeks of treatment), and 80,000 IU once every week after Week 8. The actual median weekly dose was 730.4 IU/kg in the epoetin alfa group and 850.0 IU/kg in the placebo group.

At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase. The safety results included all data from baseline through Week 52 (ie, end-of-study visit after end of treatment extension phase Week 48).

III.4.3.1.2 Adverse Events in at least 5% of subjects

A summary of key safety findings during the first 24 weeks of the study is provided in Table 15. During the first 24 weeks of the study, a numerically higher percentage of subjects in the placebo group (88.9%) reported 1 or more treatment-emergent adverse events compared with the epoetin alfa group (77.6%). At least 1 treatment-emergent adverse event leading to permanent discontinuation of study agent was reported by 10.6% of subjects in the epoetin alfa group and 13.3% of subjects in the placebo group during the first 24 weeks of the study. The percentage of subjects reporting at least 1 treatment-emergent adverse event of toxicity grade 3 or grade 4 was similar between the epoetin alfa and placebo groups (25.9% vs. 26.7%, respectively) during the first 24 weeks of the study.

25.9% of subjects in the epoetin alfa group and 17.8% in the placebo group during the first 24 weeks of the study reported treatment-emergent serious adverse events.
Two treatment-emergent serious adverse events in the epoetin alfa group were considered related to study agent by the investigator: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive (after 24 weeks of treatment).
No serious adverse event reported in the placebo group during the entire study period was considered related to study agent by the investigator.

There were a total of 8 deaths during the entire study period, 5 of these were due to treatment-emergent adverse events with onset during the first 24 weeks (4 in the epoetin alfa group [AML, sudden death, cachexia, and renal failure]; 1 in the placebo group [AML]) and 3 due to treatment-emergent adverse events with onset after Week 24 in the epoetin alfa group (congestive heart failure, sudden death, and disease progression). None of the deaths were considered related to study agent by the investigators.

Four (4.7%) subjects in the epoetin alfa group had TVEs. All 4 cases occurred during the first 24 weeks of the study; 1 (embolism [distal deep venous thrombosis]) was considered related to study agent by the investigator. No subjects in the placebo group had a TVE.

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the placebo group experienced disease progression. Among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior to or at Week 24.

After Week 24, 3 additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48).

A summary of key safety findings for the entire duration of the study is also provided in Table 15.

Table 15: Summary of Key Safety Findings for the First 24 Weeks and for the Entire Study Duration
(Study EPOANE3021: Safety Analysis Set)

	First 24 Weeks		Entire Study[a]	
	Placebo	Epoetin Alfa	Placebo	Epoetin Alfa
Analysis set: safety	45	85	45	85
Subjects reporting:				
At least 1 treatment-emergent adverse event	40 (88.9%)	66 (77.6%)	41 (91.1%)	73 (85.9%)
At least 1 treatment-emergent serious adverse event	8 (17.8%)	22 (25.9%)	10 (22.2%)	35 (41.2%)
At least 1 treatment-emergent adverse event of toxicity grade 3 or 4	12 (26.7%)	22 (25.9%)	15 (33.3%)	32 (37.6%)
At least 1 treatment-emergent adverse event leading to permanent discontinuation of study treatment	6 (13.3%)	9 (10.6%)	6 (13.3%)	15 (17.6%)
Deaths	1 (2.2%)	4 (4.7%)	1 (2.2%)	7 (8.2%)
At least 1 thrombotic vascular event	0	4 (4.7%)	0	4 (4.7%)
Disease progression (including progression to AML)	4 (8.9%)	11 (12.9%)	4 (8.9%)	14 (16.5%)
Progression to AML	2 (4.4%)	3 (3.5%)	2 (4.4%)	3 (3.5%)

[a] Includes all data from baseline through Week 52 (ie, end-of-study visit after end of treatment extension phase [Week 48]) for subjects who entered the treatment extension phase. For subjects who did not enter the treatment extension phase, an end of study visit that included safety evaluations was performed at Week 28 (ie, 4 weeks after last dose at Week 24); all data after Week 24 through Week 28 for these subjects are included in the entire study period data set. AML = acute myeloid leukemia.

Of note, the onset of treatment-emergent adverse events during the first 24 weeks (168 days) was based on actual visit dates (date of onset - baseline date + 1), whereas disease progression based on the RRC assessment using IWG 2006 criteria presented in Table 21 was based on the visit week (ie, Week 24). Therefore, in the summary tables for treatment-emergent adverse events, the number of individual treatment-emergent adverse events used by the investigators to report disease progression during the first 24 weeks of the study differs from the number of disease progressions for the same period presented in Table 21.

Assessor's comment

During the first 24 weeks of the study:

Higher percentage of subjects in the placebo group than in epoetin alfa group reported 1 or more treatment-emergent adverse events (88.9% vs. 77.6%).

Similar percentage of subjects reporting at least 1 treatment-emergent adverse event of toxicity grade 3 or grade 4 was similar between the epoetin alfa and placebo groups (25.9% vs. 26.7%).

Higher subjects in the epoetin alfa group (25.9%) than in the placebo group (17.8%) reported treatment-emergent serious adverse events.

Two treatment-emergent serious adverse events in the epoetin alfa group were considered related to study agent by the investigator: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive (after 24 weeks of treatment).

8 deaths were observed during the entire study period due to treatment-emergent adverse events (7 in the epoetin alfa group and 1 in the placebo group). None of the deaths were considered related to study agent by the investigators.

Four (4.7%) subjects in the epoetin alfa group had TVEs versus 0 in the placebo group. All 4 cases occurred during the first 24 weeks of the study.

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the placebo group experienced disease progression. Among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior to or at Week 24.
After Week 24, 3 additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48).

Finally, increases of deaths and TVE have been observed in the epoetin alfa group compared to placebo. All the safety data should be discussed regarding to the level of erythropoietin at the baseline (< or > 200UI/ml) as all responders had an erythropoietin level <200UI/ml in this study **(OM)**.

Concerning the patients presented a TVE, the MAH should document with the Hb level at the baseline, the delay and the intensity of the response to the drug, the Hb level at the response, the additional risk factor, the concomitant treatment. These informations could lead to any recommendations for the use of EPO alfa in elderly patients with additional risk **(OC)**.

In addition, in order to clarify the adverse events relative to study agent, the MAH should provide a tabulated list of adverse reactions relative or not to study agent **(OC)**.

Adverse Events in at least 5% of subjects in the First 24 Weeks

During the first 24 weeks of the study, 66 (77.6%) subjects in the epoetin alfa and 40 (88.9%) subjects in the placebo group had at least 1 treatment-emergent adverse event reported. Treatment-emergent adverse events that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group, by preferred term, were asthenia (14.1% vs. 11.1%, respectively), fatigue (9.4% vs. 6.7%), nasopharyngitis (7.1% vs. 4.4%), diarrhea and dyspnea (9.4% vs. 2.2%), constipation (7.1% vs. 0), and pruritis (5.9% vs. 0). The most frequently reported treatment-emergent adverse events by SOC and preferred term that occurred in ≥5% of the subjects during the first 24 weeks of study in either of the treatment groups are presented in Table 16.

Table 16: Treatment-Emergent Adverse Events That Occurred in the First 24 Weeks in ≥5% of the Subjects by System Organ Class and Preferred Term

(Study EPOANE3021: Safety Analysis Set - Treatment Phase Only)

	Placebo	Epoetin Alfa
Analysis set: safety – treatment phase only	45	85
Subjects reporting at least 1 treatment-emergent adverse event	40 (88.9%)	66 (77.6%)
System Organ Class [a]		
Preferred Term		
General Disorders and Administration Site Conditions	**17 (37.8%)**	**31 (36.5%)**
Asthenia	5 (11.1%)	12 (14.1%)
Fatigue	3 (6.7%)	8 (9.4%)
Pyrexia	5 (11.1%)	7 (8.2%)
Oedema peripheral	5 (11.1%)	3 (3.5%)
Infections and Infestations	**11 (24.4%)**	**24 (28.2%)**
Nasopharyngitis	2 (4.4%)	6 (7.1%)
Gastrointestinal Disorders	**8 (17.8%)**	**24 (28.2%)**
Diarrhoea	1 (2.2%)	8 (9.4%)
Constipation	0	6 (7.1%)
Metabolism and Nutrition Disorders	**4 (8.9%)**	**15 (17.6%)**
Respiratory, Thoracic and Mediastinal Disorders	**4 (8.9%)**	**13 (15.3%)**
Dyspnoea	1 (2.2%)	8 (9.4%)
Skin and Subcutaneous Tissue Disorders	**4 (8.9%)**	**12 (14.1%)**
Pruritus	0	5 (5.9%)
Musculoskeletal and Connective Tissue Disorders	**11 (24.4%)**	**11 (12.9%)**
Back pain	3 (6.7%)	1 (1.2%)
Investigations	**7 (15.6%)**	**10 (11.8%)**
Vascular Disorders	**4 (8.9%)**	**10 (11.8%)**
Blood and Lymphatic System Disorders	**7 (15.6%)**	**9 (10.6%)**
Anaemia	5 (11.1%)	5 (5.9%)

Injury, Poisoning and Procedural Complications	**5 (11.1%)**	**8 (9.4%)**
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**7 (15.6%)**	**6 (7.1%)**
Cardiac Disorders	**3 (6.7%)**	**6 (7.1%)**
Ear and Labyrinth Disorders	**3 (6.7%)**	**6 (7.1%)**
Vertigo	3 (6.7%)	4 (4.7%)
Nervous System Disorders	**6 (13.3%)**	**5 (5.9%)**
Eye Disorders	**3 (6.7%)**	**4 (4.7%)**
Reproductive System and Breast Disorders	**3 (6.7%)**	**4 (4.7%)**
Hepatobiliary Disorders	**3 (6.7%)**	**1 (1.2%)**

Note: Subjects having more than 1 event reported for a given system organ class or preferred term are counted only once for that system organ class or preferred term.

[a] Adverse events terms are coded using MedDRA/E version 14.0.

Assessor's comment

In the erythropoietin arm, the rate of treatment-emergent adverse events was much higher in the following system organ class: Gastrointestinal Disorders (17.8 vs. 28.2%), and Metabolism and nutrition disorders (8.9 vs. 17.6%), Respiratory, Thoracic and Mediastinal disorders (8.9 vs. 15.3%), Skin and subcutaneous tissue disorders (8.9 vs. 14.1%) and vascular disorders (8.9 vs. 11.8%).
Inversely, in the placebo group, the rate of treatment-emergent adverse events was higher in the following system organ class: Musculoskeletal and Connective Tissue Disorders (24.4 vs. 12.9%), Blood and Lymphatic System Disorders (15.6 vs. 10.6%), Neoplasms Benign, Malignant and Unspecified (15.6 vs. 7.1%), Nervous System Disorders were higher in the placebo group (13.3% vs 5.9%) and Hepatobiliary Disorders (6.7 vs. 1.2%).

There is no new safety signal. The most common treatment-emergent adverse events during the first 24 weeks that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group were asthenia, fatigue, nasopharyngitis, diarrhea, dyspnea, constipation, and pruritis.

Regarding of these new safety data, the MAH should discuss if the frequencies of these adverse effect remain unchanged compared with those described in the SmPC and therefore if the tabulated list of adverse reactions needs to be updated (e.g. nasopharyngitis) **(OC)**.

The MAH should also provide these data according to the stratification of EPO level (< or > 200mU/ml) at the baseline **(OC)**.

No individual treatment-emergent adverse event used by the investigators to report disease progression occurred in ≥5% of the subjects during the first 24 weeks. Individual treatment-emergent adverse events used by the investigators to report disease progression were coded as MDS (2 subjects in the epoetin group), AML (1 subject in the epoetin alfa group, 2 in the placebo group), RAEB (refractory anemia with excess blasts; 1 subject in each group), leukemia (1 subject in the epoetin alfa group), thrombocytopenia (1 subject in the epoetin alfa group), and disease progression (1 subject in the placebo group; Table 22). Therefore, based on actual visit dates, 6 (7.1%) subjects in the epoetin alfa group and 4 (8.9%) subjects in the placebo group had disease progression (based on the combined individual treatment-emergent adverse events) reported during the first 24 weeks of the study.

Adverse Events in at least 5% of subjects Entire study period

Overall during the entire study, 73 (85.9%) subjects in the epoetin alfa group and 41 (91.1%) subjects in the placebo group had a treatment-emergent adverse event. In addition to treatment-emergent adverse events in Table 16, treatment-emergent adverse events, by preferred term, that were reported in ≥5% of the subjects through the end of the study in the epoetin group were vomiting, nausea, and bone pain (each in 6 [7.1%] subjects) and abdominal pain (5 [5.9%] subjects); and in the placebo group were diarrhea, cough, and hypertension (each in 3 [6.7%] subjects).

During the entire study period, 14 (16.5%) subjects in the epoetin alfa group and 4 (8.9%) subjects in the placebo group had disease progression according to the IWG 2006 criteria. No subjects in the placebo group had disease progression after the first 24 weeks. Individual treatment-emergent adverse events used by the investigators to report disease progression after the first 24 weeks were coded as MDS (3 subjects), AML (1 subject), and disease progression (4 subjects). Therefore, based on actual visit dates, an additional 8 (9.4%) subjects in the epoetin alfa group had disease progression (based on the combined individual treatment-emergent adverse events) reported after the first 24 weeks of the study. Other than MDS in the epoetin alfa group (5 [5.9%] subjects), no individual treatment-emergent adverse event used by the investigators to report disease progression occurred in ≥5% of the subjects during the entire study period.

Assessor's comment

During the entire study, 73 (85.9%) subjects in the epoetin alfa group and 41 (91.1%) subjects in the placebo group had a treatment-emergent adverse event.

No new safety signal has been observed.

During the entire study period, higher number of subjects in the epoetin alfa (14, 16.5%) group than in the placebo group (4, 8.9%) had disease progression according to the IWG 2006 criteria.

No subjects in the placebo group had disease progression after the first 24 weeks.

Individual treatment-emergent adverse events used by the investigators to report disease progression after the first 24 weeks were coded as MDS (3 subjects), AML (1 subject), and disease progression (4 subjects). Thus, an additional 8 (9.4%) subjects in the epoetin alfa group had disease progression reported after the first 24 weeks (see more comments further in this AR).

As required above, the MAH should provide a tabulated list of all adverse reactions of the first 24 weeks and of the entire period, précising if the adverse effect is relative or not to study agent.

III.4.3.1.3 Grade 3 or 4 Adverse Events

First 24 Weeks

Grade 3 or grade 4 treatment-emergent adverse events that occurred during the first 24 weeks of the study are provided in Table 17. 22 (25.9%) subjects in the epoetin alfa and 12 (26.7%) subjects in the placebo group had at least 1 treatment-emergent adverse event of grade 3 or grade 4 toxicity reported.

No individual grade 3 or grade 4 treatment-emergent adverse event was reported in more than 1 subject except pneumonia (1 subject in the epoetin alfa group, 2 subjects in the placebo group), anemia (1 subject in each group), serum ferritin increased (2 subjects in the placebo group), and disease progression, as described below. Additionally, grade 3 or grade 4 thrombocytopenia was reported in 1 subject in each group; for the subject in the epoetin alfa group, this was the treatment-emergent adverse event used by the investigator to report disease progression, described below.

Individual grade 3 or grade 4 treatment-emergent adverse events used by the investigators to report disease progression during the first 24 weeks of the study (based on actual dates) were coded as MDS (2 subjects in the epoetin group), AML (1 subject in each group), RAEB (1 subject in each group), leukemia (1 subject in the epoetin alfa group), thrombocytopenia (1 subject in the epoetin alfa group), and disease progression (1 subject in the placebo group; Table 22).

Table 17: Treatment-Emergent Adverse Events of Toxicity Grade 3 or 4 That Occurred in the First 24 Weeks

(Study EPOANE3021: Safety Analysis Set - Treatment Phase Only)

	Placebo	Epoetin Alfa
Analysis set: safety – treatment phase only	45	85
Subjects reporting at least 1 treatment-emergent adverse event of toxicity grade 3 or 4	12 (26.7%)	22 (25.9%)

System Organ Class [a]		
Preferred Term		
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**3 (6.7%)**	**6 (7.1%)**
Myelodysplastic syndrome	0	2 (2.4%)
Acute myeloid leukaemia	1 (2.2%)	1 (1.2%)
Refractory anaemia with an excess of blasts	1 (2.2%)	1 (1.2%)
Leukaemia	0	1 (1.2%)
Prostate cancer	0	1 (1.2%)
Basal cell carcinoma	1 (2.2%)	0
Infections and Infestations	**2 (4.4%)**	**5 (5.9%)**
Pneumonia	2 (4.4%)	1 (1.2%)
Sinusitis	0	1 (1.2%)
Soft tissue infection	0	1 (1.2%)
Tooth abscess	0	1 (1.2%)
Urosepsis	0	1 (1.2%)
Blood and Lymphatic System Disorders	**2 (4.4%)**	**3 (3.5%)**
Anaemia	1 (2.2%)	1 (1.2%)
Thrombocytopenia	1 (2.2%)	1 (1.2%)
Neutropenia	0	1 (1.2%)
Gastrointestinal Disorders	**1 (2.2%)**	**3 (3.5%)**
Abdominal pain	0	1 (1.2%)
Diarrhoea	0	1 (1.2%)
Gastritis	0	1 (1.2%)
Ileitis	0	1 (1.2%)
Oesophagitis	0	1 (1.2%)
Vomiting	0	1 (1.2%)
Toothache	1 (2.2%)	0
Vascular Disorders	**1 (2.2%)**	**2 (2.4%)**
Embolism	0	1 (1.2%)
Systolic hypertension	0	1 (1.2%)
Aortic dissection	1 (2.2%)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**2 (2.4%)**
Back pain	0	1 (1.2%)
Pain in extremity	0	1 (1.2%)
Investigations	**4 (8.9%)**	**1 (1.2%)**
Blood pressure increased	0	1 (1.2%)
Serum ferritin increased	2 (4.4%)	0
Haemoglobin decreased	1 (2.2%)	0
Lymphocyte count decreased	1 (2.2%)	0
Neutrophil count decreased	1 (2.2%)	0
White blood cell count decreased	1 (2.2%)	0
Injury, Poisoning and Procedural Complications	**0**	**1 (1.2%)**
Traumatic brain injury	0	1 (1.2%)
Metabolism and Nutrition Disorders	**0**	**1 (1.2%)**

Diabetes mellitus	0	1 (1.2%)
General Disorders and Administration Site Conditions	**2 (4.4%)**	**0**
Disease progression	1 (2.2%)	0
Pyrexia	1 (2.2%)	0
Cardiac Disorders	**1 (2.2%)**	**0**
Arrhythmia	1 (2.2%)	0
Psychiatric Disorders	**1 (2.2%)**	**0**
Depression	1 (2.2%)	0

Note: Subjects having more than 1 event reported for a given system organ class or preferred term are counted only once for that system organ class or preferred term.

[a] Adverse events terms are coded using MedDRA/E version 14.0.

Assessor's comment

Grade 3 or 4 treatment-emergent adverse events were reported for similar percentages of subjects in the epoetin alfa and placebo groups (25.9% and 26.7%, respectively); subjects had at least one event.

No individual grade 3 or grade 4 treatment-emergent adverse event was reported in more than 1 subject in either group except pneumonia (1 subject in the epoetin alfa group, 2 subjects in the placebo group), anemia (1 subject in each group), thrombocytopenia (1 subject in placebo group; see below for additional subject in epoetin alfa group), serum ferritin increased (2 subjects in the placebo group), and combined individual treatment-emergent adverse events used by the investigators to report disease progression (MDS in 2 subjects in the epoetin group; AML and RAEB, each in 1 subject in each group; leukemia and thrombocytopenia, each in 1 subject in the epoetin alfa group, and disease progression in 1 subject in the placebo group).

Entire study period

Overall during the entire study, 32 (37.6%) subjects in the epoetin alfa group and 15 (33.3%) subjects in the placebo group had at least 1 grade 3 or grade 4 treatment-emergent adverse event. In addition to the grade 3 or 4 treatment-emergent adverse events in Table 17, neutropenia (2 [2.4%] subjects; 1 in the first 24 weeks and 1 after 24 weeks) and disease progression (as described below) were reported in 2 or more subjects in the epoetin alfa group through the end of the study; no additional grade 3 or 4 treatment-emergent adverse event was reported in more than 1 subject through the end of the study.

Individual grade 3 or grade 4 treatment-emergent adverse events used by the investigators to report disease progression after the first 24 weeks of the study for subjects in the epoetin alfa group (based on actual dates) were coded as MDS (2 subjects), AML (1 subject), and disease progression (1 subject; Table 22).

Assessor's comment

Percentages of subjects with grade 3 or 4 treatment-emergent adverse events were in the same range between the two groups (37.6% and 33.33%).

III.4.3.1.4 Deaths, other serious adverse events, and other significant adverse events

Deaths

Four (4.7%) subjects in the epoetin alfa group and 1 (2.2%) subject in the placebo group had at least 1 treatment-emergent adverse event with onset during the first 24 weeks, which resulted in death during or after the first 24 weeks. One subject in each group died due to AML and the other 3 deaths in the epoetin alfa group were due to sudden death, cachexia, and renal failure.

There were 3 more deaths in the epoetin alfa group that were due to treatment-emergent adverse events with onset after the first 24 weeks of the study: 1 death occurred during the 4-week follow-up period after Week 24, congestive cardiac failure; and 2 deaths occurred due to a treatment-emergent adverse event with onset during the treatment extension phase, sudden death and disease progression.

The deaths due cachexia, congestive heart failure, and disease progression in the epoetin alfa group and AML in the placebo group all occurred more than 30 days after the last dose of study agent.

None of the deaths was considered by the investigators to be related to study agent.

Subjects who died during the study are summarized in Table 18.

Table 18: Deaths

(Study EPOANE3021: Safety Analysis Set - Treatment Phase Only)

Treatment Group	Subject ID Age/Sex	Verbatim/ Preferred Term/ System Organ Class	Start Day	Toxicity Grade[a]	Relation to Study Agent[b]	Day of Death	AE Responsible for Termination
Deaths that occurred due to treatment-emergent events with onset in the first 24 weeks							
Epoetin Alfa	73/Male	Cachexia/ Cachexia/ Metabolism and nutrition disorders	98	5	1	203	No
	71/Female	Sudden death/ Sudden death/ General disorders and administration site conditions	45	5	1	45	Yes
	66/Male	Progressive AML/ Acute myeloid leukaemia/ Neoplasms benign, malignant and unspecified (incl cysts and polyps)	86	4	1	164	Yes
	94/Male	Kidney insufficiency/ Renal failure/ Renal and urinary disorders	91	5	1	108	Yes
Placebo	75/Male	Evolution in AML/ Acute myeloid leukaemia/ Neoplasms benign, malignant and unspecified (incl cysts and polyps)	62	5	1	149	Yes
Deaths that occurred due to treatment-emergent adverse events with onset after Week 24							
Epoetin Alfa	69/Female	Atypical progression with skin specific lesions Disease progression General disorders and administration site conditions	176	5	1	332	No
	89/Male	Sudden death/ Sudden death/ General disorders and administration site conditions	304	5	1	304	Yes
	87/Male	Congestive heart failure/ Cardiac failure congestive/	193	3	1	201	No

Cardiac disorders	

Note: Adverse events terms are coded using MedDRA/E version 14.0.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0: 1 = Mild, 2 = Moderate , 3 = Severe or medically significant but not immediately lifethreatening, 4 = Life-threatening consequences,
5 = Death related to AE

[b] 1 = Not Related, 2 = Doubtful, 3 = Possible, 4 = Probable, 5 = Very Likely

AML = acute myeloid leukemia.

Brief narratives for deaths are provided by the MAH.

Deaths that occurred due to treatment-emergent events with onset in the first 24 weeks:

- **Epoetin alfa treatment**:

  - Subject , a 73-year-old man died on Day 203 of the study, approximately 6 weeks after the last dose of study agent at Week 23, due to cachexia after approximately 4 months of frequent vomiting after food ingestion and anorexia leading to reduced food intake and significant weight loss. The subject had been hospitalized several times during the course of the study. Endoscopic investigations revealed gastritis and esophagitis; however, there was no evidence of malignancy on biopsy. The event of cachexia was considered not related to study agent. Additional details on this subject regarding TVE (ischemic stroke) are provided further in this AR.

  - Subject , a 71-year-old woman died at home (sudden death) on Day 45 of the study, 2 days after her Week 6 dose of study agent. The woman was unresponsive in the morning and the blood pressure had dropped to 90/60 mmHg; no request for paramedic assistance was made. A few hours later, the subject died. An autopsy was not performed and the cause of death was unknown. The primary physician indicated that the subject may have had a stroke; however, there was no confirmed diagnosis. The event was considered serious and not related to study agent by the investigator. This event was considered a TVE, additional details are provided further in this AR;

  - Subject , a 66-year-old man with RCMD at baseline was diagnosed with AML on Day 86 of the study, approximately 2 weeks after his Week 10 dose of study agent. Bone marrow examination indicated 90% blasts and there were 45% blasts in the peripheral blood. The subject discontinued study agent due to progression to AML and was withdrawn from the study. The subject was unresponsive to salvage chemotherapy, had persistence of blast cells after induction, and on Day 164 of the study, approximately 3 months after his last dose of study agent, the subject died due to progressive AML. The event was considered not related to study agent. Additional details for disease progression in this subject are provided in Table 21

  - Subject , a 94-year-old man with a history of renal insufficiency (compensated), had treatment-emergent renal insufficiency reported on Day 91. The subject subsequently died due to renal failure on Day 108 of the study, 26 days after his last dose of study agent at Week 11 (Week 12 dose was withheld). The event was considered not related to study agent.

- **Placebo**

  Subject , a 75-year-old man with RAEB-1 at baseline was reported to have died due to AML on Day 149 of the study. On Study Day 45, the subject had fever, and

was hospitalized with a serious adverse event of pneumonia. On the same day, a nonserious adverse event of thrombocytopenia was reported (platelet count not reported). Myelodysplastic syndrome was considered as the risk factor and suspected cause. A bone marrow biopsy was performed with results indicating 20% of blasts and evolution to AML on Day 62 of the study. The study agent was discontinued due to this event (last dose at Week 6), and he was subsequently withdrawn from the study. The subject died approximately 3 months after progression to AML and approximately 3.5 months after his last dose of study agent. The event was not considered related to study treatment. Additional details for disease progression in this subject are provided in Table 22.

Deaths that occurred due to treatment-emergent adverse events with onset after Week 24:

- **Epoetin alfa treatment**:

  - Subject , a 69-year-old woman developed atypical progression with skin specific lesions (preferred term: disease progression) on Day 176 of the study. Skin biopsy from the lesions suggested an infiltrate related to MDS. At Week 24, there were no signs of progression in the bone marrow, but there was leukocytosis and thrombocytopenia noted in the hematology panel. An unscheduled hematology test taken 1 week after Week 24 revealed worsening of the leukocytosis and thrombocytopenia. In the context of the specific skin lesion, atypical disease progression with skin-specific lesions was reported and considered by the investigator as not related to study agent. Treatment with azacitidine and hydroxyurea was initiated 2 weeks after the last study visit, which resulted in disappearance of the skin lesions. Approximately 4 months after the last study visit, the subject's condition deteriorated and she was hospitalized with severe leukocytosis and pulmonary leukostasis. She did not respond to the cytoreducing therapy with increased doses of hydroxyurea and mercaptopurine and died from cardiorespiratory arrest due to pulmonary leukostasis in the context of acute change of MDS (probably to AML type M4, although this was not confirmed by bone marrow test) approximately 5.5 months after her last dose of study agent.

  - Subject , an 89-year-old man with a history of hypertension and cerebral atherosclerosis died suddenly at home on Day 304 of the study, 2 days after his last dose of study agent at Week 43. No autopsy was performed and the reason for the death was unknown. The event was considered not related to epoetin alfa.

  - Subject , an 87-year-old man with a cardiovascular history including atrial fibrillation, hypertension, and acute coronary syndrome was diagnosed with congestive heart failure on Day 193 and subsequently died due to this event on Day 201 of the study, 31 days after his last dose of study agent at Week 24. The event was considered not related to epoetin alfa.

Assessor's comment

Deaths are considered not related to study agent by investigators.

However,

in the subject , a73-year-old-man, investigation of cachexia revealed an old ischemic infarct considered doubtfully related to study agent.

In subject , a 71-year-old woman died at home (sudden death), 2 days after her Week 6 dose of study agent. The cause of death was unknown. The primary physician indicated that the subject may have had a stroke; however, there was no confirmed diagnosis. The event was not related to study agent by the investigator.

In subject , a 94-year-old man with a history of renal insufficiency (compensated), had treatment-emergent renal insufficiency reported on Day 91. The subject subsequently died due to renal failure on Day 108 of the study, 26 days after his last dose of study agent at Week 11. The event was considered not related to study agent.

In subject , an 89-year-old man with a history of hypertension and cerebral atherosclerosis died suddenly at home on Day 304 of the study, 2 days after his last dose of study agent at Week 43. No autopsy was performed and the reason for the death was unknown. The event was considered not related to epoetin alfa.

In Subject , an 87-year-old man with a cardiovascular history including atrial fibrillation, hypertension, and acute coronary syndrome was diagnosed with congestive heart failure on Day 193 and subsequently died due to this event on Day 201 of the study, 31 days after his last dose of study agent at Week 24. The event was considered not related to epoetin alfa.

The MAH should propose some recommendations for the use of EPO alfa in elderly patients with comorbidities **(OC).**

Serious adverse events

During the first 24 weeks of the study, there were 22 (25.9%) subjects in the epoetin alfa group and 8 (17.8%) subjects in the placebo group who had at least 1 serious treatment-emergent adverse event reported (Table 19). No individual serious adverse event was reported for more than 1 subject except pneumonia (2 subjects in each group), pyrexia (2 subjects in the epoetin alfa group, 1 subject in the placebo group), and those related to disease progression, as described below.

One treatment-emergent serious adverse event (embolism [distal deep venous thrombosis]) in the epoetin alfa group was considered related to study agent and led to interruption of study agent during the first 24 weeks of treatment.

All subjects who experienced disease progression during the first 24 weeks of the study had it reported as a treatment-emergent serious adverse event (based on actual dates); 6 (7.1%) subjects in the epoetin alfa group and 4 (8.9%) subjects in the placebo group. Individual treatment-emergent serious adverse events used by the investigators to report disease progression were coded as MDS (2 subjects in the epoetin group), AML (1 subject in the epoetin alfa group, 2 in the placebo group), RAEB (1 subject in each group), leukemia (1 subject in the epoetin alfa group), thrombocytopenia (1 subject in the epoetin alfa group), and disease progression (1 subject in the placebo group; Table 22).

Table 19: Treatment-Emergent Serious Adverse Events That Occurred in First 24 weeks
(Study EPOANE3021: Safety Analysis Set - Treatment Phase Only)

	Placebo	Epoetin Alfa
Analysis set: safety – treatment phase only	45	85
Subjects reporting at least 1 treatment-emergent serious adverse event	8 (17.8%)	22 (25.9%)
System Organ Class [a]		
Preferred Term		
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**3 (6.7%)**	**6 (7.1%)**
Myelodysplastic syndrome	0	2 (2.4%)
Acute myeloid leukaemia	2 (4.4%)	1 (1.2%)
Refractory anaemia with an excess of blasts	1 (2.2%)	1 (1.2%)
Leukaemia	0	1 (1.2%)
Prostate cancer	0	1 (1.2%)
Infections and Infestations	**2 (4.4%)**	**5 (5.9%)**
Pneumonia	2 (4.4%)	2 (2.4%)
Soft Tissue Infection	0	1 (1.2%)
Tooth Abscess	0	1 (1.2%)
Urosepsis	0	1 (1.2%)

General Disorders and Administration Site Conditions	**2 (4.4%)**	**4 (4.7%)**
Pyrexia	1 (2.2%)	2 (2.4%)
Chest pain	0	1 (1.2%)
Sudden death	0	1 (1.2%)
Disease progression	1 (2.2%)	0
Gastrointestinal Disorders	**1 (2.2%)**	**4 (4.7%)**
Abdominal pain	0	1 (1.2%)
Gastritis	0	1 (1.2%)
Ileitis	0	1 (1.2%)
Nausea	0	1 (1.2%)
Oesophagitis	0	1 (1.2%)
Vomiting	0	1 (1.2%)
Pancreatitis acute	1 (2.2%)	0
Injury, Poisoning and Procedural Complications	**0**	**4 (4.7%)**
Femur fracture	0	1 (1.2%)
Injury	0	1 (1.2%)
Laceration	0	1 (1.2%)
Traumatic brain injury	0	1 (1.2%)
Vascular Disorders	**1 (2.2%)**	**2 (2.4%)**
Embolism	0	1 (1.2%)
Temporal arteritis	0	1 (1.2%)
Aortic dissection	1 (2.2%)	0
Metabolism and Nutrition Disorders	**0**	**2 (2.4%)**
Cachexia	0	1 (1.2%)
Hyperglycaemia	0	1 (1.2%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**2 (2.4%)**
Dyspnoea	0	1 (1.2%)
Pleural effusion	0	1 (1.2%)
Blood and Lymphatic System Disorders	**0**	**1 (1.2%)**
Thrombocytopenia	0	1 (1.2%)
Renal and Urinary Disorders	**0**	**1 (1.2%)**
Renal failure	0	1 (1.2%)
Skin and Subcutaneous Tissue Disorders	**0**	**1 (1.2%)**
Neuropathic ulcer	0	1 (1.2%)
Social Circumstances	**0**	**1 (1.2%)**
Elderly	0	1 (1.2%)
Surgical and Medical Procedures	**0**	**1 (1.2%)**
Knee arthroplasty	0	1 (1.2%)
Cardiac Disorders	**1 (2.2%)**	**0**
Arrhythmia	1 (2.2%)	0
Investigations	**1 (2.2%)**	**0**
Haemoglobin decreased	1 (2.2%)	0

[a] Adverse events terms are coded using MedDRA/E version 14.0

Note: Subjects having more than 1 event reported for a given system organ class or preferred term are counted only once for that system organ class or preferred term.

Overall during the entire study period, 35 (41.2%) subjects in the epoetin alfa group and 10 (22.2%) subjects in the placebo group had at least 1 treatment-emergent serious adverse event. No additional treatment-emergent serious adverse event was reported in more than 1 subject through the end of the study except sudden death and knee arthroplasty (each in 2 [2.4%] subjects; 1 during the first 24 weeks and 1 after 24 weeks (Table 19) and those related to disease progression in the epoetin alfa group, as described below.

The only treatment-emergent serious adverse event reported in ≥5% of subjects in either group during the entire study period was MDS (5 [5.9%] subjects in the epoetin alfa group). For subjects in the epoetin alfa group, individual treatment-emergent serious adverse events used by the investigators to report disease progression after the first 24 weeks were coded as MDS (3 subjects), AML (1 subject), and disease progression (4 subjects; Table 22). Therefore, based on actual visit dates, an additional 8 (9.4%) subjects in the epoetin alfa group had disease progression (based on the combined individual treatment-emergent serious adverse events) reported after the first 24 weeks of the study.

Thirteen (15.3%) subjects from the epoetin alfa group and 6 (13.3%) subjects from the placebo group experienced at least 1 treatment-emergent serious adverse event during the entire study period, which led to permanent discontinuation of study agent. The majority of treatment-emergent serious adverse events in both treatment groups, which led to permanent discontinuation of study agent, were individual treatment-emergent serious adverse events used by the investigators to report disease progression (ie, MDS, AML, RAEB, leukemia, disease progression, thrombocytopenia).

In addition to the 1 related treatment-emergent serious adverse event during the first 24 weeks of the study (embolism [distal deep venous thrombosis]), anti-erythropoietin antibody positive was reported for a subject in the epoetin alfa group after the first 24 weeks of the study that was considered related to study agent and led to permanent discontinuation of study agent. For this subject, there were no signs of PRCA reported in the bone marrow; serum erythropoietin remained detectable and reticulocytes were normal at the last available measurement.

None of the reported serious adverse events in the placebo group were considered related to study agent.

Assessor's comment

During the first 24 weeks of the study,

Higher number of subjects in the epoetin alfa group than in the placebo group (22 (25.9%) 8 (17.8%) had at least 1 serious treatment-emergent adverse event reported.

Two treatment-emergent serious adverse events in the epoetin alfa group were considered related to study agent: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive (after 24 weeks of treatment).

Subjects who had serious adverse events related to study agent during the study are described below:

Serious adverse event related to study agent that occurred in the first 24 weeks:

- **Epoetin alfa treatment**:

  Subject , a 77-year-old woman had a treatment-emergent serious adverse event of embolism (distal deep venous thrombosis in the lower leg, diagnosed with doppler) on Day 126 of the study, 6 days after the most recent dose of study agent (Week 17); last hemoglobin of 12.8 g/dL. The subject was hospitalized on the same day and was treated with phenprocoumon and enoxaparin sodium. The event was considered by the investigator to be very likely related to study agent and treatment with the study agent was interrupted. The event resolved on Day 133 of the study. Upon event resolution the subject continued her participation in the trial until Week 48 with study agent being withheld when necessary due to safety considerations (hemoglobin level >11.0 g/dL).

Serious adverse event related to study agent that occurred after Week 24:

- **Epoetin alfa treatment**:

  Subject , a 63-year-old man had a treatment-emergent serious adverse event of anti-erythropoietin antibody positive (grade 1) on Day 169 (Week 24 visit) of the study. The results of the radioimmunoprecipitation test from the sample collected at the Week 24 visit were positive for anti-erythropoietin antibodies (1:20, 1.0% counts per minute [cpm] [a positive antibody is ≥0.9% cpm in the assay]) and at the early termination visit on Day 197 (1:20, 1.5% cpm). For all other titration levels, the cpms were below the thresholds for positivity at both visits. Hemoglobin values were 10.8 g/dL on Day 160, 11.1 g/dL on Day 169, 11.3 g/dL on Day 175, 10.8 g/dL on Day 182, 10.7 g/dL on Day 197, and 9.5 g/dL on Day 226 (follow-up visit).

  Reticulocytes were 23.94 $\times 10^9$/L on Day 169, 49.95 $\times 10^9$/L on Day 197, and 20.79 $\times 10^9$/L on Day 226. There were no signs of PRCA reported in the bone marrow; serum erythropoietin remained detectable and reticulocytes were normal at the last available measurement. The event was considered by the investigator to be very likely related to study agent and the study agent was discontinued due to this event (last study agent dose at Week 27 [Day 190]). The last reported outcome of the event was not resolved.

III.4.3.1.5 Other Significant Adverse Events

Adverse Events Leading to Discontinuation of Study Agent

First 24 Weeks

During the first 24 weeks of the study, 9 (10.6%) subjects in the epoetin alfa group and 6 (13.3%) subjects in the placebo group experienced at least 1 treatment-emergent adverse event leading to discontinuation of study agent (Table 20). No individual treatment-emergent adverse event leading to study agent discontinuation was reported for more than 1 subject except those related to disease progression, as described below.

Individual treatment-emergent adverse events used by the investigators to report disease progressions that led to discontinuation of study agent were coded as MDS (1 subject in the epoetin alfa group), AML (1 subject in the epoetin alfa group, 2 in the placebo group), RAEB (1 subject in each group), leukemia (1 subject in the epoetin alfa group), thrombocytopenia (1 subject in the epoetin alfa group), and disease progression (1 subject in the placebo group).

Table 20: Treatment-Emergent Adverse Events Leading to Permanent D Treatment That Occurred in the First 24 Weeks of the Study

(Study EPOANE3021: Safety Analysis Set - Treatment Phase Only)

	Placebo	Epoetin Alfa
Analysis set: safety – treatment phase only	45	85
Subjects reporting at least 1 treatment-emergent adverse event leading to permanent discontinuation of study treatment	6 (13.3%)	9 (10.6%)
System Organ Class [a]		
Preferred Term		
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**3 (6.7%)**	**5 (5.9%)**
Acute myeloid leukaemia	2 (4.4%)	1 (1.2%)
Refractory anaemia with an excess of blasts	1 (2.2%)	1 (1.2%)
Leukaemia	0	1 (1.2%)
Myelodysplastic syndrome	0	1 (1.2%)
Prostate cancer	0	1 (1.2%)
General Disorders and Administration Site Conditions	**2 (4.4%)**	**1 (1.2%)**
Sudden death	0	1 (1.2%)
Disease progression	1 (2.2%)	0
Pyrexia	1 (2.2%)	0
Vascular disorders	**1 (2.2%)**	**1 (1.2%)**
Phlebitis	0	1 (1.2%)
Aortic dissection	1 (2.2%)	0
Blood and Lymphatic System Disorders	**0**	**1 (1.2%)**

Thrombocytopenia	0	1 (1.2%)
Renal and Urinary Disorders	**0**	**1 (1.2%)**
Renal failure	0	1 (1.2%)

[a] Adverse events terms are coded using MedDRA/E version 14.0

Note: Subjects having more than 1 event reported for a given system organ class or preferred term are counted only once for that system organ class or preferred term.

Assessor's comment

Nine (10.6%) subjects in the epoetin alfa group discontinued treatment due to adverse event compared with 6 (13.3%) subjects in the placebo group.

No individual treatment-emergent adverse event leading to study agent discontinuation was reported for more than 1 subject except those related to disease progression.

Entire Study Period

Fifteen (17.6%) subjects from the epoetin alfa group and 6 (13.3%) subjects from the placebo group had treatment-emergent adverse events leading to study agent discontinuation at any time during the entire study period. In addition to the treatment-emergent adverse events leading to study agent discontinuation in Table 20, the following occurred in the epoetin alfa group through the end of the study: disease progression in 2 subjects (Table 22), and sudden death, hematuria, acute porphyria, and anti-erythropoietin antibody positive, each in 1 subject. No subject in the placebo group had a treatment-emergent adverse event leading to study agent discontinuation after the first 24 weeks of the study.

Adverse events leading to discontinuation of study agent in the first 24 weeks:

- **Epoetin alfa treatment**:

  Subject , a 78-year-old man with pancytopenia at baseline and RCMD had an event of severe thrombocytopenia on Day 64 (Week 9) of the study that was considered serious and not related to study agent. The subject received study agent at Week 8 and then the dose was withheld at Week 9 and discontinued due to this event; the subject was withdrawn from the study. The platelet count was 35×10^9/L at Week 8, 14×10^9/L at Week 9, and 11×10^9/L at early termination visit (10 days after Week 9). Following a bone marrow aspirate, progression to RAEB-2 was confirmed. The last dose of study agent was administered at Week 8. The outcome of the event was reported as not resolved. Additional details for disease progression in this subject are provided in Table 22.

  Subject , a 75-year-old woman with a history of superficial thrombophlebitis had an event of phlebitis (doppler confirmed distal, deep venous

thrombosis) on Day 7 of the study that was considered doubtfully related to study agent. Study agent was discontinued due to this event and the subject was withdrawn from the study; the only dose of study agent was administered on Day 1. The outcome of the event was reported as not resolved. Additional details on this TVE are provided in the section III.4.3.1.6.

- Subject , an 84-year-old man with a history of prostate hypertrophy was diagnosed with prostate cancer on Day 158 (approximately 2 weeks after Week 20 visit) of the study that was considered serious and not related to study agent. His last dose of study agent was at Week 4, after which his dose was held from Week 5 (hemoglobin 13.2 g/dL) through Week 20 (14.1 g/dL). Approximately 6 weeks after his Week 20 visit, he was withdrawn from the study. The outcome of the event was reported as not resolved.

- Subject , sudden death; see brief narrative in section III.4.3.1.6.

- Subject , a 75-year-old man with pancytopenia and RAEB-1 at baseline had disease progression (leukemia, grade 3) on Day 120 of the study that was considered serious and not related to study agent. The last dose of study agent was administered at Week 16; the subject discontinued study agent due to this event and was withdrawn from the study. The outcome of the event was reported as not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , death due to AML; see Table 22.

Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 68-year old woman with RCMD at baseline had disease progression (RAEB-2) on Day 50 (Week 8) of the study that was considered serious and not related to study agent. Disease progression was diagnosed based on a peripheral blood sample that showed 13% blasts; bone marrow sample that confirmed the disease progression was taken 1 month later. The last dose of study agent was administered at Week 11 and she was withdrawn from the study 1 week later. Additional details for disease progression in this subject are provided in Table 22.

- Subject , death due renal failure; see Table 18.

- Subject , a 67-year-old woman with RCMD at baseline had disease progression to RAEB-2 (grade 3) on Day 97 of the study that was considered serious and not related to study agent; the onset of the event was reported 3 days after her Week 13 dose of study agent. The subject received 2 additional doses and then study agent was discontinued due to this event. The outcome of the event was reported as unknown. Additional details for disease progression in this subject are provided in Table 22.

- **Placebo treatment**

- Subject , an 82-year-old man had an event of persistent high fever (pyrexia; grade 3) on Day 123 of the study that was considered serious and not related to

study agent; the onset of the event was reported as 5 days after his Week 17 dose of study agent. The subject received 1 additional dose and then study agent was discontinued due to this event and suspicion of disease progression. However disease progression was not confirmed for this subject, although during hospitalization, the subject received numerous transfusions for treatment of anemia and thrombocytopenia. The event resolved on Day 156 of the study following extensive antibiotic therapy.

- Subject , death due to AML. Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 70-year-old woman with a history of hypertension had a hypertension crisis that was followed by an aortic dissection (grade 4) on Day 58 (1 day after Week 8 dose) of the study that was considered serious and not related to study agent. The subject had study agent discontinued and was withdrawn from the study due to this event. The outcome of the event was reported as not resolved.

- Subject , a 77-year-old man with RA at baseline had disease progression (grade 3, RAEB-1) on Day 118 (5 days after Week 16 dose) of the study. He had study agent discontinued due to this event and was withdrawn from the study. The event was considered serious and not related to study agent. The outcome of the event was reported as not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 79-year-old man with RCMD and pancytopenia at baseline progressed to RAEB-1 (grade 3) on Day 104 (5 days after Week 14 dose), that was considered serious and doubtfully related to study agent. The study agent was discontinued and the subject was withdrawn from the study due to this event. The outcome of the event was reported as not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 54-year-old woman with RCMD at baseline progressed to AML (grade 4) on Day 41 (5 days after Week 5 dose) of the study. The event was considered serious and not related to study agent. The study agent was discontinued and the subject was withdrawn from the study due to this event. The outcome of the event was reported as not resolved. Additional details for disease progression in this subject are provided in Table 22.

Adverse events leading to discontinuation of study agent that occurred after Week 24:

- **Epoetin alfa treatment**:

  - Subject , a 79-year-old woman with RCMD-RS at baseline had disease progression (the subject became transfusion dependent, there were no signs of progression in the bone marrow) on Day 311 (Week 44) that was considered serious and not related to study agent; the last dose of study agent was administered at Week 43. Study agent was discontinued and the subject was withdrawn from the study due to this

event. The outcome was reported as not recovered/not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 64-year-old man with RCMD at baseline had disease progression (to RAEB-1) on Day 335 (Week 48) of the study that was considered serious and not related to study agent. Bone marrow progression was noted with delay by the site, as the subject was responding to therapy and was enrolled in the open-label phase. Study agent was discontinued and the subject was withdrawn from the study due to this event. The outcome was reported as not recovered/not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , a 90-year-old man with RCMD at baseline had progression of MDS (to RAEB-2) on Day 169 (Week 24) of the study that was considered serious and not related to study agent; the subject was withdrawn from the study as a non-responder and the disease progression was a finding from the bone marrow aspirate required at Week 24. The outcome was reported as not recovered/not resolved. Additional details for disease progression in this subject are provided in Table 22.

- Subject , sudden death; see Table 18.

- Subject , a 73-year-old woman had a serious adverse event of hematuria (grade 2) on Day 204 (7 days after her Week 28 study agent dose). She had thrombocytopenia since her inclusion in the study (screening, 51 10^9/L; baseline, 114 10^9/L), which deteriorated (platelets were 4 10^9/L at Week 24 and 18 10^9/L at Week 28) before the onset of hematuria. Study agent was discontinued and the subject was withdrawn from the study due to this event. The event resolved after 1 week (Day 211) and was not considered by the investigator to be related to study agent.

- Subject , a 72-year-old man had an event of acute porphyria (grade 1) with onset on Day 175 (Week 25). The subject's last dose of study agent was at Week 31; he had study agent discontinued due to the ongoing adverse event and was withdrawn from the study at Week 32. The event was not considered by the investigator to be related to study agent.

- Subject , anti-erythropoietin antibody positive.

III.4.3.1.6 Adverse Events of Clinical Interest

Thrombotic Vascular Events

During the first 24 weeks of the study, 4 (4.7%) subjects from the epoetin alfa group had thrombotic vascular events TVEs (sudden death, ischemic stroke, embolism [distal deep venous thrombosis], and phlebitis [distal deep venous thrombosis]) compared with none in the placebo group. Three events were confirmed as TVEs (ischemic stroke, embolism, and phlebitis) and one (embolism) was considered related to study agent by the investigator. Stroke was considered as a

possible cause by the investigator as the reason for the sudden death; however, this was not confirmed and was not reported as an adverse event. Two subjects had significant risk factors: the subject who had ischemic stroke had a medical history of atrial fibrillation and congestive heart failure, and the subject who had phlebitis had a medical history of superficial thrombophlebitis. Ischemic stroke was reported after a computed tomography (CT) scan of the brain (performed during a hospitalization for investigation of cachexia) revealed an old ischemic infarct in the subcortical white matter. One subject had a response to epoetin alfa at the time of the TVE (embolism).

There were no TVEs reported in either treatment group after Week 24 of the study.

Thrombotic vascular events that occurred in the first 24 weeks:

Epoetin alfa group:

- Subject , a 73-year-old man with a history of atrial fibrillation and cardiac failure who was receiving anticoagulant therapy had a CT scan of the brain performed on Day 105 (7 days after Week 14 dose) during a hospitalization for investigation of cachexia that revealed an old ischemic infarct (preferred term: ischemic stroke) in the subcortical white matter that was considered doubtfully related to study agent by the investigator. The subject continued in the study and subsequently died due to cachexia. The subject's baseline hemoglobin was 7.1 g/dL and he was a non-responder at the time of the event (hemoglobin ranged from 6.1 to 8.4 g/dL from Week 1 through Week 12, and at Week 14 was 6.7 g/dL).

- Subject , who had a history of superficial thrombophlebitis, had phlebitis (doppler confirmed distal deep venous thrombosis) on Day 7 of the study that was considered doubtfully related to study agent by the investigator and resulted in discontinuation of study agent (only 1 dose received). The subject's hemoglobin was 8.1 g/dL at screening, 11.0 g/dL at baseline (Day 1), and 10.8 g/dL at early termination (Day 16).

- Subject , sudden death; see brief narrative. The primary physician indicated that the subject may have had a stroke; however, there was no confirmed diagnosis. The sudden death event was considered serious and not related to study agent by the investigator. The subject's baseline hemoglobin was 7.8 g/dL, ranged from 8.1 to 9.3 g/dL from Week 1 through Week 5, and was 9.1 g/dL at Week 6 (2 days prior to death).

- Subject , embolism (distal deep venous thrombosis) was considered serious and very likely related to study agent. This subject had an erythroid response for 8 weeks (Week 12 to Week 20) and the event occurred during the period of response with a hemoglobin value of 12.8 g/dL on the day of the event.

Assessor's comment

There were 4 (4.7%) subjects in the epoetin alfa group with TVEs (sudden death, ischemic stroke, embolism [distal deep venous thrombosis], and phlebitis [distal deep venous thrombosis]); all TVEs occurred during the first 24 weeks of the study.

Three events were confirmed as TVEs: two considered doubtfully related to study agent (ischemic stroke, embolism, and phlebitis) and one (embolism) was considered related to study agent by the investigator.

As required above, the MAH should provide a tabulated list of all adverse events of the first 24 weeks and of the entire period, specifying if the adverse effect is relative or not to study agent. Adverse effects doubtfully, possibly, probably, very likely relatives to study agent should be considered as relative to study agent **(OC)**.

Also, the MAH should document for all patients presented a TVE the Hb level at the baseline, the delay and the intensity of the response to the drug, the Hb level at the response, the additional risk factor, the concomitant treatment. These informations could lead to any recommendations for the use of EPO alfa in elderly patients with additional risk **(OC)**.

Disease Progression

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the placebo group experienced disease progression as defined (Table 21).

Among the subjects who experienced disease progression, there were 5 who progressed to AML: 3 (3.5%) in the epoetin alfa group and 2 (4.4%) in the placebo group (Table 21). All progressions to AML during the study occurred prior or at Week 24. . The disease progression to other non-AML classes was shown in 8 (9.4%) subjects in the epoetin alfa group and 2 (4.4%) subjects in the placebo group during the first 24 weeks. This numerically higher percentage of subjects with disease progression to other non-AML classes in the epoetin alfa group was not considered to be a major safety concern, since this is consistent with the expected underlying disease development and is not considered a malignant progression.

Table 21: Myelodysplastic Syndrome Progression Including Transformation to Acute Myeloid Leukemia in the EPOANE3021 Study

(EPOANE3021: Safety Analysis Set)

	Total MDS progression		Progression to AML		Progression to other non-AML classes	
	Placebo	Epoetin Alfa	Placebo	Epoetin Alfa	Placebo	Epoetin Alfa
Analysis set: safety	45	85	45	85	45	85
In first 24 weeks (total)	4 (8.9%)	11 (12.9%)	2 (4.4%)	3 (3.5%)	2 (4.4%)	8 (9.4%)
Week 8	0	1 (1.2%)	-	-	0	1 (1.2%)
Week 16	1 (2.2%)	1 (1.2%)	-	-	1 (2.2%)	1 (1.2%)
Week 24	0	5 (5.9%)	0	1 (1.2%)	0	4 (4.7%)
Subjects who had disease progression at Early Withdrawal on or before Week 24	3 (6.7%)	4 (4.7%)	2 (4.4%)	2 (2.4%)	1 (2.2%)	2 (2.3%)
After 24 weeks (total)*	0	3 (3.5%)	0	0	0	3 (3.5%)
Week 44	0	1 (1.2%)	0	0	0	1 (1.2%)
Week 48	0	2 (2.4%)	0	0	0	2 (2.4%)
Entire study (total)**	4 (8.9%)	14 (16.5%)	2 (4.4%)	3 (3.5%)	2 (4.4%)	11 (12.9%)

Note: Disease progression is defined as according to the International Working Group (IWG) Response Criteria 2006.

After Week 24, 3 (3.5%) additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48). Therefore, during the entire study period, 14 (16.5%) subjects in the epoetin alfa group experienced disease progression at any time during the study. No subjects progressed to AML after Week 24.

Summary of Subjects Who had Disease Progression

A summary of subjects who had disease progression is provided in Table 22. Overall, the majority of subjects who had disease progression had <5% blasts, were intermediate-1 IPSS risk category, and had a WHO subclass of RCMD at baseline. With the exception of 2 subjects in the epoetin alfa group, all subjects had a ≥50% increase in the percentage of bone marrow blasts at the time of progression. At the time of disease progression, 2 subjects in the epoetin alfa group had no change from baseline in IPSS risk category and WHO subclass, 2 subjects in each group had no change from baseline in IPSS risk category but had an increase in severity of the WHO subclass, and the remainder of subjects in each group had an increase in severity from baseline in both the IPSS risk category and WHO subclass.

Assessor's comment

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the placebo group experienced disease progression based on the RRC assessment using IWG 2006 criteria. Among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior or at Week 24. After Week 24, 3 additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48).

Table 22: Summary of Subjects Who Had Disease Progression

Subject Number/ Age at Time of Progression/ Sex	Weeks From BL to Progression (IWG 2006 criteria)/ Progression to AML	AE PT/Toxicity Grade[a]/Study Agent Discontinued Due to AE	Change in Bone Marrow Blast %[b]	Change in IPSS[c]	Change in WHO class[d]	Disease progression response	Presence of ≥20% blasts	Disease Progression Details Chosen
Epoetin alfa group								
65/ Female	24/ No	MDS/ Grade 2/ No	Aspirate: 2 TO 5	INT-1 = 0.5 To 1.0 TO INT-1 = 0.5 To 1.0	RA TO RAEB-1	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		At least 50% decrement in platelets; A decrease in platelets to 20,000/mm^3; Reduction in hemoglobin by >2 g/dL
76/ Male	24/ No	Disease progression/ Grade 3/No	Aspirate: 3 TO 6	Low = 0 TO INT-1 = 0.5 To 1.0	RCMD TO RAEB-1	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		50% decrement in granulocyte
80/ Female	44/ No	Disease progression/ Grade 2/Yes	Aspirate: 2 TO 0	Low = 0 TO Low = 0	RCMD-RS TO RCMD-RS			Transfusion dependence
79/ Male	10/ No	Thrombo-cytopenia/ Grade 3/Yes	Biopsy: 1 TO 18 Aspirate: 1 TO 17	INT-1 = 0.5 To 1.0 TO INT-2 = 1.5 To 2.0	RCMD TO RAEB-2	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		At least 50% decrement in platelets; A decrease in platelets to 20,000/mm^3
70/ Female	25/ No	Disease progression[e]/ Grade 5/No	Aspirate: 4 TO 3	INT-1 = 0.5 To 1.0 TO INT-1 = 0.5 To 1.0	RCMD TO RCMD			
66/ Male	47/ No	Disease progression/ Grade 2/Yes	Aspirate: 0 TO 5-6	Not done TO INT-1 = 0.5 To 1.0	RCMD TO RAEB-1	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		
79/ Male	24/ Yes	AML/ Grade 4/ No	Biopsy: 7 TO 50 Aspirate: 3 TO 30	INT-1 = 0.5 To 1.0 TO High = ≥2.5	RAEB-1 TO AML	5%-10% blasts: ≥50% increase to >10% blasts	Yes	50% decrement in granulocyte; A decrease in granulocytes to 500/mm^3; Increase of IPSS subtype to INT-2 or higher and INT to poor risk karyotype
53/ Male	10/ No	MDS/ Grade 3/No (Withdrew consent)	Biopsy: 14 TO ND Aspirate: 9 TO 11	INT-1 = 0.5 To 1.0 TO High = ≥2.5	RAEB-1 TO RAEB-2	5%-10% blasts: ≥50% increase to >10% blasts		Increase of IPSS subtype to INT-2 or higher and good risk to INT or poor risk karyotype
76/ Male	18/ Yes	Leukemia/ Grade 3/ Yes	Biopsy: ND TO 30.58 Aspirate: 6 TO 22	INT-1 = 0.5 To 1.0 TO High = ≥2.5	RAEB-1 TO AML	5%-10% blasts: ≥50% increase to >10% blasts	Yes	

66/ Male	12/ Yes	AML/ Grade 4/ Yes	Biopsy: 0 TO ND Aspirate: 1 TO 90	INT-1 = 0.5 To 1.0 TO High = ≥2.5	RCMD TO AML	Less than 5% blasts: ≥50% increase in blasts to >5% blasts	Yes	
68/ Female	8/ No	MDS[f]/ Grade 3/ Yes	Biopsy: 4 TO ND Aspirate: ND TO 13 TO	INT-1 = 0.5 To 1.0 High = ≥2.5	RCMD TO RAEB-2	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		Increase of IPSS subtype to INT-2 or higher and good risk to INT or poor risk karyotype
68/ Female	16/ No	RAEB/ Grade 3/ Yes	Biopsy: 2 TO 7 Aspirate: 4 TO 10	INT-1 = 0.5 To 1.0 TO Not done	RCMD TO RAEB-2	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		Increase of IPSS subtype to INT-2 or higher and INT to poor risk karyotype
72/ Male	48/ No	No MDS/ Grade 4/ No	Aspirate: 1 TO 10	INT-1 = 0.5 To 1.0 TO INT-1 = 0.5 To 1.0	RCMD TO RAEB-2	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		
91/ Male	24/ No	MDS/ Grade 4/ No	Aspirate: 4 TO 15	Low = 0 TO INT-2 = 1.5 To 2.0	RCMD TO RAEB-2	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		50% decrement in granulocyte; A decrease in granulocytes to 500/mm^3; At least 50% decrement in platelets; Transfusion dependence
Placebo group								
76/ Male	11/ Yes	AML/ Grade 5/ Yes	Biopsy: 7 TO 25 Aspirate: 5 TO 20	INT-1 = 0.5 To 1.0 TO High = ≥2.5	RAEB-1 TO AML	5%-10% blasts: ≥50% increase to >10% blasts	Yes	At least 50% decrement in platelets; A decrease in platelets to 20,000/mm^3; Transfusion dependence; Increase of IPSS subtype to INT-2 or higher and INT to poor risk karyotype
78/ Male	16/ No	Disease progression[g]/ Grade 3/Yes	Biopsy: 0 TO ND Aspirate: 0 TO 6.5	INT-1 = 0.5 To 1.0 TO INT-1 = 0.5 To 1.0	RA TO RAEB-1	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		
80/ Male	14/ No	RAEB/ Grade 3/ Yes	Biopsy: 0 TO ND Aspirate: 0 TO 5.5	INT-1 = 0.5 To 1.0 TO INT-1 = 0.5 To 1.0	RCMD TO RAEB-1	Less than 5% blasts: ≥50% increase in blasts to >5% blasts		
54/ Female	6/ Yes	AML/ Grade 4/ Yes	Biopsy: <5 TO 70 Aspirate: ND TO 30 TO	Low = 0 High = ≥2.5	RCMD TO AML	Less than 5% blasts: ≥50% increase in blasts to >5% blasts	Yes	

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0: 2 = moderate, 3 = severe or medically significant but not immediately life-threatening, 4 = life-threatening consequences, 5 = death related to AE.

[b] Change in bone marrow blasts (%) at screening and at progression.

[c] Change in IPSS at screening and at progression.

[d]

Change in WHO class at screening and at progression.

[e] Verbatim: atypical progression with skin-specific lesions. Disease progression was diagnosed based on blood sample taken 6 days after the Week 24 visit, showing progressing leukocytosis in the context of specific skin lesions; although disease progression in this subject did not meet IWG 2006 criteria, the investigator determined that the event was proof of progression. Disease progression for this subject was included in summary of disease progressions that occurred at Week 24.

[f] Subject - disease progression was diagnosed based on peripheral blood sample that showed 13% blasts, bone marrow sample that confirmed the disease progression was taken 1 month later.

[g] Verbatim: progress to RAEB-1.

AE PT = adverse event preferred term; AML = acute myeloid leukemia; BL = baseline; MDS = myelodysplastic syndromes; INT = intermediate; IPSS = International Prognostic Scoring System; IWG = International Working Group; RA = refractory anemia; ND = not done; RAEB = refractory anemia with excess blasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = refractory cytopenia with multilineage dysplasia with ringed sideroblasts; WHO = World Health Organization.

III.4.3.1.7 Clinical Laboratory Evaluation

Hemoglobin and reticulocyte changes during the study were assessed as part of the efficacy results. There was a statistically significant ($p<0.001$ at all weeks except Week 8, $p=0.002$) improvement observed in mean erythrocyte counts over time in the epoetin alfa group from baseline through Week 24 compared with the placebo group. There were no statistically significant differences between the 2 treatment groups in mean platelet or leukocyte counts over time from baseline through Week 24.

No clinically notable differences were observed with regard to changes in the clinical chemistry laboratory parameters.

Serum ferritin, serum iron, total iron binding capacity, and transferrin saturation values were similar between both the treatment groups at baseline (screening visit). Mean decreases in serum iron were observed in the epoetin alfa group compared with mean increases in the placebo group. No other clinically notable differences were observed with regard to changes in these parameters.

The majority of clinically significant laboratory abnormalities were low hemoglobin levels, and low erythrocyte, reticulocyte, or platelet counts. Of note, 1 subject in the epoetin alfa group had a serious adverse event of anti-erythropoietin antibody positive reported after Week 24 of the study.

III.4.3.1.8 Vital Signs and Physical Findings

Overall, a numerically higher percentage of subjects in the placebo group compared with the epoetin alfa group (23 [51.1%] subjects vs. 35 [41.2%] subjects) had vital signs beyond clinically important limits at any time point of measurement. One (2.2%) subject in the epoetin alfa group and 2 (4.4%) subjects in the placebo group had systolic blood pressure values beyond clinically important limits at any time point. Likewise, 18 (21.2%) subjects from epoetin alfa group and 13 (28.9%) subjects from placebo group had diastolic blood pressure values beyond clinically important limits at any time point. There were no subjects who had pulse rate values beyond clinically important limits. Twenty-four (28.2%) subjects from the epoetin alfa group and 11 (24.4%) subjects from the placebo group had BMI values beyond clinically important limits at any time point of measurement.

One subject in the epoetin alfa group had a grade 3 non-serious treatment-emergent adverse event of blood pressure increased which was considered possibly related to study agent. The event had no impact on dosing of study agent and the event resolved with concomitant treatment. Four (4.7%) subjects in the epoetin alfa group and 3 (6.7%) subjects in the placebo group had non-serious treatment-emergent adverse events of hypertension; most of these events were grade 1 or 2. One subject in each treatment group experienced Grade 3 hypertension: the subject in the epoetin alfa group had systolic hypertension reported at Day 8 that resolved same day and was considered not related to study agent based on the investigator's assessment; the subject in the

placebo group had hypertension reported at Day 196 (7 days after last dose of study agent) that was a worsening of a pre-existing condition, resolved the next day, and was considered not related to study agent based on the investigator's assessment. No subject had a change in study agent dose due to hypertension. All events resolved except 1 in each treatment group (both were Grade 1). All hypertension events were considered not related to study agent with exception of 2 Grade 1 events (1 in each treatment group) and 1 Grade 2 event in the placebo group.

III.4.3.2 Supportive study: EPOANE3018 study

The primary objective of this study was to demonstrate that epoetin alfa treatment reduces the proportion of anemic subjects with IPSS low- or intermediate-1-risk MDS who require transfusion, compared with placebo, through Week 48. Due to poor subject enrollment, the study was terminated early (from 14 January 2009 to 01 March 2010). Therefore, with a final enrollment of only 25 subjects (8 in placebo group, 8 in epoetin alfa 40,000 IU group, and 9 in epoetin alfa 80,000 IU group), it was difficult to draw any clinically relevant efficacy or safety conclusions from this study. Due to this reason, in the safety section below, results of EPO-ANE-3018 study will be only briefly summarized when appropriate.

The safety population was defined as all subjects who were randomly assigned to a treatment group and who received at least 1 dose of study drug. As only limited data were collected, only descriptive statistics were provided.

Thirteen white men and 12 white women with a median age of 74.0 years were enrolled. All 25 subjects had an Eastern Cooperative Group (ECOG) score of 0 or 1. At baseline, most subjects were in the refractory anemia (RA) (11 subjects) or refractory anemia with ringed sideroblasts (RARS) (8 subjects) groups based on the WHO MDS Classification system and most subjects were also in the RA (16 subjects) and RARS (9 subjects) groups based on the French-American-British (FAB) MDS Classification system. The subject IPSS Classification was either Low (17 subjects) or Intermediate-1 (8 subjects). Six of the subjects had MDS-related anemia transfusions at baseline. The median baseline hemoglobin concentration was 8.80 g/dL.

III.4.3.2.1Patient exposure

Of the 25 treated subjects in the safety analysis, 8 in the epoetin alfa 40,000 IU group, 9 in the epoetin alfa 80,000 IU group and 8 subjects received placebo. The median weekly dose was 38,750.0 IU in the epoetin alfa 40,000 IU group, 65,434.78 IU in the epoetin alfa 80,000 IU group, and 77,440.48 IU in the placebo group. The median exposure was 10.64 weeks for the placebo group, 10.00 weeks for the epoetin alfa 40,000 IU group, and 22.86 weeks for the epoetin alfa 80,000 IU group.Two of the 25 subjects met the definition for completing the entire study. Of the 23 subjects who discontinued the study, 19 of these discontinued due to premature closing of the study.

III.4.3.2.2Adverse events

The overall adverse event profile during the Treatment Phase and Safety Assessment Phase is presented in Table 23. During the Treatment Phase, treatment-emergent adverse events were reported for 7 (88%) of 8 subjects in the placebo group, 6 (75%) of 8 subjects in the epoetin alfa 40,000 IU group, and 7 (78%) of 9 subjects in the epoetin alfa 80,000 IU group. The most commonly reported adverse events were fatigue (20%, 5/25, of total subjects), asthenia (16%, 4/25), nausea (12%, 3/25), anemia (12%, 3/25), and upper respiratory infection (12%, 3/25). Most of the TEAEs were mild and mild or moderate in severity, and either not related or doubtfully related to the study drug. No new safety signals or adverse drug reactions (ADRs) were detected for the 17 subjects receiving epoetin alfa in this study.

Table 23: Overall Summary of Adverse Events During the Treatment Phase and Safety Assessment Phase (Study EPO-ANE-3018: Safety Analysis Set).

Events	Placebo (N=8) n (%)	Epoetin alfa 40000 IU (N=8) n (%)	Epoetin alfa 80000 IU (N=9) n (%)
During treatment phase	**8**	**8**	**9**
Subjects with any treatment-emergent adverse events	7 (88)	6 (75)	7 (78)
Subjects with any treatment-emergent adverse event related to AML, MDS or transfusion complications	3 (38)	2 (25)	2 (22)
Subjects with drug related treatment-emergent adverse events	2 (25)	1 (13)	1 (11)
Subjects with serious treatment-emergent adverse events	2 (25)	2 (25)	4 (44)
Subjects with treatment-emergent adverse events leading to treatment discontinuation	2 (25)	0	0
Number of subjects who died during treatment phase	0	0	0
During safety assessment phase	**5**	**5**	**6**
Subjects with serious adverse events	0	0	0
Subjects with any adverse event related to AML, MDS or transfusion complications	0	0	0
Number of subjects who died during safety assessment phase	0	0	0

Note: Percentages calculated with the number of subjects in each group during each phase as denominator.
AML=acute myeloid leukemia; MDS=myelodysplastic syndromes
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III.4.3.2.1. Serious adverse events and deaths

Serious adverse events were reported for 2 (25%) of 8 subjects in each of the placebo and epoetin alfa 40,000 IU groups, and for 4 (44%) of 9 subjects in the epoetin alfa 80,000 IU group.

Most of the severe (Grade 3) and life threatening (Grade 4) adverse events occurred in the Blood and Lymphatic System classification.

All serious adverse events were considered by the investigator to be not related to study drug, with the exception of 1 serious adverse event of PRCA in the placebo group, which was considered possibly related (while investigator was still blinded to treatment allocation).

Two subjects, both in the placebo group, had adverse events that led to their discontinuation of study drug. Subject was diagnosed with prostate cancer 1 day after his first dose and Subject was reported to have PRCA, previously discussed above.

There were no TVEs in this study.

Three (38%) subjects in the placebo group, 2 (25%) subjects in the epoetin alfa 40,000 IU group, and 2 (22%) subjects in the epoetin alfa 80,000 IU group were reported to have adverse events related to MDS, AML, or transfusion complications. One subject ( ) in the epoetin alfa 80,000 IU treatment group was assessed by the investigator as having MDS disease progression based on RBC transfusion dependency. However, central pathology review of the bone marrow assessment could not confirm MDS disease progression.

During the Safety Assessment Phase there were no serious adverse events or events related to AML, MDS, or transfusion complications.

No subjects died during the Treatment or Safety Assessment Phases.

III.4.3.2.2. Laboratory findings

Although changes from baseline in laboratory values varied across parameters and treatment groups, clinical interpretation is difficult due to the small number of subjects in each treatment group (<10 subjects in each group).

III.4.3.2.3. Safety in special populations

The MAH did not provide new safety data in special populations from this study.

Assessor's comment

The primary objective of this study was to evaluate epoetin alfa efficacy in anemic subjects with IPSS low- or intermediate-1-risk MDS who require transfusion, compared with placebo, through Week 48.

Due to poor subject enrollment, the study was terminated early. Only 25 subjects were enrolled (8 in placebo group, 8 in epoetin alfa 40,000 IU group, and 9 in epoetin alfa 80,000 IU group). Thus, only safety data were commented by the MAH.

Two of the 25 subjects met the definition for completing the entire study. Of the 23 subjects who discontinued the study, 19 of these discontinued due to premature closing of the study.

During the Treatment Phase, treatment-emergent adverse events were reported for 7 (88%) of 8 subjects in the placebo group, 6 (75%) of 8 subjects in the epoetin alfa 40,000 IU group, and 7 (78%) of 9 subjects in the epoetin alfa 80,000 IU group.

The most commonly reported adverse events were fatigue (20%, 5/25, of total subjects), asthenia (16%, 4/25), nausea (12%, 3/25), anemia (12%, 3/25), and upper respiratory infection (12%, 3/25).

No new safety signals.

Serious adverse events were reported for 2 (25%) of 8 subjects in each of the placebo and epoetin alfa 40,000 IU groups, and for 4 (44%) of 9 subjects in the epoetin alfa 80,000 IU group.

There were no TVEs in this study.

Three (38%) subjects in the placebo group, 2 (25%) subjects in the epoetin alfa 40,000 IU group, and 2 (22%) subjects in the epoetin alfa 80,000 IU group were reported to have adverse events related to MDS, AML, or transfusion complications.

During the Safety Assessment Phase there were no serious adverse events or events related to AML, MDS, or transfusion complications.

No subjects died during the Treatment or Safety Assessment Phases.

III.4.3.3 . Supportive studies: MDS Registry Studies

III.4.3.3.1. Patient exposure

French MDS Registry Study

In 142 patients received EPREX, the initial dose was reported between 4,000 IU and 80,000 IU with the most frequent dose of 40,000 IU (in 70.4% of patients).

Italian MDS Registry Study

Of the 1,049 patients included in the analysis, 335 were treated with EPO 40,000 IU/week to 80,000 IU/week. Treatment duration for non-responders was 12 weeks and for the responders was until relapse or MDS progression.

Spanish MDS Registry Study

Of the 722 patients with evaluable data, 530 patients received ESAs and 192 patients received transfusion support. Of the 530 ESAs-treated patients, about half (243 [45.8%]) of the patients received darbepoetin alpha and the other received other erythropoietins, and 24 patients (4.5%) received EPREX. In general the epoetin dose was between 10,000 IU/week and 80,000 IU/week.

III.4.3.3.2. Adverse events

The safety data in the MDS registry studies are mainly focused on the disease progression to AML. The collection of other safety related information is generally incomplete.

French MDS Registry Study

Seven patients stopped the treatment for secondary effects. The majority of secondary effects were headache (3 cases) and hypertension (2 cases), two patients presented pruritus.

During evolution, 11 patients presented a transformation in AML. The median duration of survival after transformation was 8 months (1-18 months).

Four patients presented a transformation during the treatment by Eprex and 7 after the interruption of the treatment.

- Patients who presented a transformation during the treatment by Eprex:

- Four patients transformed: 3 RAEB1 and one unclassified MDS.

- The karyotype was normal in 3 cases, one with -7 (secondary MDS).

- Delay in transformation was 2 months in 3 patients and 10 months in one patient.

- Patients who presented a transformation after interruption of Eprex treatment:

7 patients presented an evolution in AML in a median of 21 months after interruption of Eprex treatment (5 – 53 months):

- 6 were primary MDS and one secondary.

- Karyotype was normal in 4, one loss of the Y, one del 5q and one trisomy 8.

- According to WHO classification: 2 RAEB1, 2 RCMD, 1 ARS, 1 5q- syndrome, 1 MDS unclassified.

Italian MDS Registry Study

Among the 1,049 patients, only 52 (5%) patients showed a leukemic evolution. There appeared to be a higher incidence of leukemic evolution in non-EPO-treated patients over the EPO alpha treated patients (p=0.05), but the number of events was too low to draw any conclusions.

Spanish MDS Registry Study

Patients in this study receiving treatment with ESA did not appear to have a higher incidence of disease progression to AML (13.7% in patients treated with ESAs and 15.8% in RBC transfusion support group). Treatment responders appeared to have a lower risk of AML transformation (at 5 years, 13% responders developed AML vs. 28% non-responders developed AML; p=0.0007); since start of ESA at 5 years: 20% vs 37%, p<0.0001).

Assessor's comment

In the French registry (without placebo group), the tolerance was good and most patients could receive the totality of the treatment. In this cohort of patients, the risk of acute leukaemia is about 7%, which is aligned with known incidence in IPSS Low or Int-1 risk population.

In Italian registry, any statistical difference in leukemic evolution rate in treated versus untreated patients were observed. The authors concluded that no potential leukemic risk could be attributed to EPO alpha therapy.

In Spanish registry, patients in this study receiving treatment with ESA did not appear to have a higher incidence of disease progression to AML (13.7% in patients treated with ESAs and 15.8% in RBC transfusion support group). However, the report did not focus the evaluation of disease progression in the 25 patients treated by EPO alfa.

The data registers and prospective studies seemed to be mature enough to ensure patient safety, including the risk of acutisation.

III.5 Product information

III.5.1 Summary of Product Characteristics

The application concerns an update to the Summary of Product Characteristics (SmPC) of EPREX®/ERYPO® to add the new indication:
EPREX, ERYPO is indicated for the treatment of anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS).

This update involves the following proposed changes:

- The addition of a sentence in section 4.1 of the SmPC:

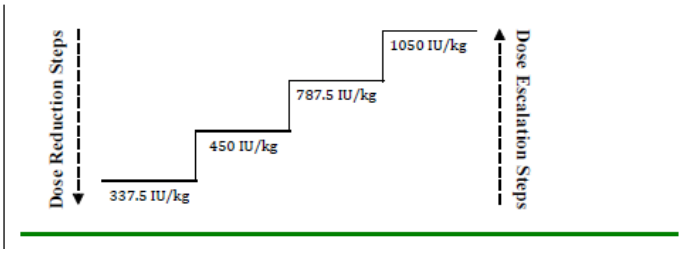
EPREX, ERYPO is indicated for the treatment of anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS).

- The addition of a paragraph in section 4.2 of the SmPC:

EPREX, ERYPO should be administered to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L).

The recommended starting dose is EPREX, ERYPO 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week.

It is recommended that response be assessed at week 8. If no erythroid response is achieved after 8 weeks according to IWG 2006 criteria (see section 5.1- *Pharmacodynamic properties – Clinical efficacy and safety*), and the haemoglobin concentration is below 11 g/dL (6.8 mmol/L), the dose should be increased from 450 IU/kg once every week to 1050 IU/kg once every week (maximum dose is 80,000 IU per week).
Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). See diagram below for guidelines for stepwise dose adjustment. Epoetin alfa should be withheld or the dose reduced when the haemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Upon dose reduction, if haemoglobin concentration drops ≥1g/dL the dose should be increased.



A sustained haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.

In addition, an addition of a sentence relative to method of administration:
EPREX, ERYPO should be administered as a subcutaneous injection.

- The addition of a sentence in section 4.8 of the SmPC:

The safety profile for patients with low- or intermediate-1-risk MDS treated with EPREX, ERYPO was consistent with the known safety profile of EPREX, ERYPO. No new Adverse Drug Reactions were identified in studies in patients with MDS.

- The addition of a paragraph in section 5.1 of the SmPC:

A randomized, double-blind, placebo-controlled, multicenter study evaluated the efficacy and safety of epoetin alfa in adult anemic subjects with low- or intermediate-1-risk MDS.

Erythroid response was defined according to IWG 2006 criteria as a haemoglobin increase ≥ 1.5 g/dL from baseline or a reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline, and a response duration of at least 8 weeks.

Erythroid response during the first 24 weeks of the study was demonstrated by 27/85 (31.8%) of the subjects in the epoetin alfa group compared to 2/45 (4.4%) of the subjects in the placebo group ($p<0.001$).

Time to first transfusion was statistically significantly longer in the treatment group ($p=0.046$).

The percentage of subjects who were transfused in the treatment group decreased from 51.8% in the 8 weeks prior to baseline to 24.7% between weeks 16 and 24, compared to the placebo group which increased from 48.9% to 54.1% over the same time period.

Assessor's comment

Concerning the EPOANE 3021 study, the MAH should mention in section 5.1 that all of the responding subjects were in the strata with serum erythropoietin less than 200 mU/ml during screening and also the higher rate of TVE in the epoietin alfa group than in placebo group in EPOANE 3021 study.

In addition, the MAH should justify the (very short) dosing recommendations proposed for section 4.2, which cover only a part of the dosing recommendations used during the study (CSP

section 6) and are thus considered insufficient and confusing, and align accordingly (comment).

SmPC section 4.8 should be updated with new data from pivotal study EPOANE3021, i.e. including information about patients treated for MDS in the introductory paragraph "Of a total 3,262 subjects in 23 randomised,… studies,…" and any further concerned paragraph (comments).

III.5.2 Package leaflet and user test

The following additions the Patient Information Leaflet (PIL) have been proposed by the MAH:

1. What EPREX is and what it is used for

EPREX is used to treat anaemia in adults with myelodysplastic syndromes. EPREX can reduce the need for a blood transfusion.

3. How to use EPREX

Adults with myelodysplastic syndrome

- Your doctor may initiate treatment with EPREX if your haemoglobin is 10 g/dL or less.
- EPREX is given by injection under the skin.
- The starting dose is 450 IU per kilogram bodyweight once a week.
- Your doctor will order blood tests, and may adjust the dose, depending on how your anaemia responds to EPREX treatment.
- Your doctor will maintain your haemoglobin level between 10 and 12 g/dL as a high
- haemoglobin level may increase the risk of blood clots and death.

Assessor's comment

The RMS has no comment regarding the sections 1 and 3 of the PIL.

In the section 2: "What do you need to know before you see EPREX"; in the paragraph "Take special care with EPREX": the MAH should propose some warnings as it was recommended to patients with chronic renal failure.

No user test has been provided by the MAH.

III.5.3 Labelling

The MAH does not propose any modification of labelling.

III.6 Risk Management Plan

The MAH does not propose any measure of risk minimisation. The safety evaluation in this procedure was focussed on the risk of acute myeloid leukemia (AML) in low-or intermediate-1 myelodysplastic syndromes (MDS) exposed to erythropoiesis-stimulating agents (ESA).

Four studies examining this risk have been provided by the MAH:

- EPOANE3021 study (randomised, double-blind, placebo-controlled (2:1 randomisation) phase 3 study): document No: EDMS-ERI-98387941; 1.0
- French MDS registry study: document "EPREX® the GFM experience"
- Italian MDS registry study: document "Report on erythropoietin alpha treatment in MDS: a survey from the FISM Italian registry" dated 15 October 2013
- Spanish MDS registry study: document GESMD-SPRESAS-2012-01

We summarised results from these studies in table below:

Study	Comparison groups	Duration of follow-up	Results
EPOANE3021	82 **EPO-alpha** vs 45 placebo	2 years	3 (3.5%) vs 2 (4.4%)
French MDS registry	142 **EPO-alpha**	Median follow-up: 6.4 years	11 presented a transformation in AML
Italian MDS registry	335 (32%) **EPO-alpha** vs 714 (68) non-EPO	Maximum follow-up: approximately 16.6 years	Higher incidence in **non-EPO** treated patients (p=0.05); however, the number of events is low and the difference between curves is minimal.
Spanish MDS registry	530 **EPOs** vs 192 non-EPO	Median follow-up: 3.1 vs 2.4 years	No statistical difference between both groups

As of June 2016, EPO-alpha has not yet been indicated in the treatment of anaemia in low-or intermediate-1 MDS. However, it has been used for years for this purpose in real-world setting.
From these studies, we can conclude that the risk of AML is not statistically different between EPO-alpha and non-EPO groups neither at short-term nor at long-term follow-up. Based on these results, at this stage, it seems not necessary to request a PASS to the MAH.

III.7 Assessment on similarity

The MAH has produced this similarity assessment report for the current Type II variation requesting the additional indication for epoetin alfa: Treatment of anaemia (haemoglobin

concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS). Orphan designation has not been requested for epoetin alfa in this indication.

Article 8(1) of Regulation (European Commission; EC) No 141/2000 requires that where a marketing authorization in respect of an orphan medicinal product is granted either by centralized procedure or in all Members States, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product (so-called 10-year market exclusivity). According to Article 3 of Regulation (EC) No 847/2000, the definition of similar medicinal product is "a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product and which is intended for the same therapeutic indication". The definition of "similar active substance" according to Article 3 is "an identical active substance, or an active substance with the same principal molecular features (but not necessarily all of the same molecular features) and which acts via the same mechanism".

According to the EMA list of Orphan Designations searched 8 March 2016, there are six active substances that have a positive orphan designation in the condition of 'Treatment of myelodysplastic syndromes'. Of these substances, only two have been approved in the EU and they are the only agents that have been granted orphan status and are approved for marketing in the EU for these indications.

Vidaza (azacitidine) is approved for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with intermediate-2 and high risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS).

Revlimid (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

1. Mechanism of action

The MAH´s position

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. EPO is the key regulator of red blood cell production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation.

Azacitidine, as a pyrimidine nucleoside analogue designed to incorporate into RNS and DNA instead of cytidine, azacitidine has a broad spectrum of antimetabolic effects. The primary

pharmacodynamics effects in the treatment of MDS are inhibition of DNS methylation and cytotoxicity by incorporation of azacitidine.

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, proerythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of proinflammatory cytokines (e.g., TNF-αand IL-6) by monocytes.

2. Molecular structure

The MAH´s position

Recombinant human EPO (epoetin alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO.
Azacitidine (Vidaza) is a pyrimidine nucleoside analogue of cytidine, 4-Amino-1-β-Dribofuranosyl-1,3,5-triazin-2(1H)-one.
Lenalidomide (Revlimid) is a small molecule 3-(4'Aminoisoindoline-1'-one)-1-piperidine-2,6-dione, C13H13N3O3.
The structures of azacitidine and lenalidomide share no obvious similarities with the structure of epoetin alfa.

Assessor's comment

It is acknowledged that the main molecular targets and pharmacodynamics effects are different between erythropoietin, azacitidine and lenalidomide. Erythropoietin and those both orphan drugs approved are not similar from a mechanism of action point of view.
In addition, the molecular structure of epoetin alfa (glycoprotein hormone) is significantly different from those of the other orphan products (small chemical structures) approved in the EU for the treatment of patients with MDS.
Based on the structural differences, and the differences in the mechanisms of action of epoetin alfa and the other orphan-designated agents approved for the treatment of patients with MDS (azacitidine and lenalidomide), the RMS does agree with the MAH that epoetin alfa is not similar to those orphan-designated products.

IV. DISCUSSION

Myelodysplastic syndromes are clonal marrow stem-cell disorders, characterized by ineffective hemopoiesis leading to blood cytopenias, and by progression to acute myeloid leukemia (AML) in one third of patients. The syndromes are most common in elderly people. The natural course of MDS is highly variable, with survival ranging from a few weeks to several years.

Anemia is a major contributor to the symptomatology of MDS and is associated with fatigue, weakness, shortness of breath, and comorbidity. For patients with lower-risk MDS, cytopenias are a predominant feature and are associated with significant deterioration. Hematologic and quality of life improvement are important therapeutic goals.

Since the use of hypomethylating agents is associated with significant toxicity, these are currently utilized predominantly for patients with advanced stages of MDS (e.g. Vidaza®). Revlimid was approved in low- or intermediate-1-risk MDS but the indication was restricted to a relatively narrow population: transfusion-dependent patients with an isolated deletion 5q cytogenetic abnormality. Additional treatment options are needed for patients with earlier stages of MDS.

Since transfusion dependence negatively affects survival in patients with MDS, epoetin alfa treatment might reduce or avoid transfusion and ultimately provide a survival benefit. Therefore, the MAH submitted in this procedure the EPOANE 3021 controlled study to evaluate treatment in this patient population.

Baseline demographics were comparable between the treatment groups concerning age, sexe, BMI. There was a higher percentage of subjects with an IPSS risk category of intermediate-1 in the epoetin alfa group but not statistically significant. The population included was in accordance with the pathology and the stages of the disease.

The prognostic score IPPS was revised from the start of the study (23 June 2011) and its analysis in March 2016 and called IPPS-R. Changes in patients distribution in this score, in particularly between score IPSS-R intermediate and high have been observed. However, this scoring change should not impact the efficacy and safety profile of EPREX in this population.

The primary efficacy parameter is defined by the demonstration of ER according to IWG 2006 criteria at any time during the first 24 weeks of the study. The percentage of the responders in the epoetin alfa group (n=85) was significantly higher compared with the placebo group (n=45) at any time during the first 24 weeks (31.8% vs. 4.4%; $p<0.001$). It is unclear if Hb were based on untransfused patients within the previous week of Hb assessment or any transfusion prior to week 24. However, the RRC has individually re-evaluated the ER of each subject taking into account the stability of the response and exclude Hb measurements considered due to

transfusion. The approach chosen by the MAH seems reasonable. The higher rate of erythroid response in epoetin alfa group than in placebo group was confirmed at Week 24 with the response review committee (RRC).

20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 7/31 (22.6%) subjects with prior transfusions (two subjects with prior transfusion reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline). The difference of responses rates between subjects with or without prior transfusions was added in the SmPC.

Screening serum erythropoietin concentration of less than 500 mU/ml was required among the inclusion criteria. A difference in erythroid response rate was observed between subjects with baseline serum erythropoietin < 200 mU/mL and those ≥200 mU/mL (31.8% vs 0%). Thus, all of the responding subjects were in the strata with serum erythropoetin less than 200 mU/mL during screening. Due to the small size in patients who have Hb levels less than 8 g/dL at baseline and are already transfusion dependent in EPOANE 3021 study, it is not possible to conclude the benefit of the drug in this subgroup of patients. Basing on these data, only a serum erythropoietin less than 200 mU/ml should be considered as a restriction in EPREX indication.

The comparison of time to first RBC transfusion between the treatment groups was analyzed by the Kaplan-Meier analysis. The epoetin alfa group begins to show separation from the placebo group at approximately Week 4 for the probability of being transfusion free. Higher statistically significant difference in time to first RBC transfusion after Week 4 in the epoetin alfa group compared with the placebo group (median= 142 vs. 50.0 days; p=0.007) has been observed with the HR of 2.029 (1.194, 3.451). Epoietin alfa had an impact on time to first RBC transfusion after 4 weeks of treatment, which is consistent with the mode of action of epoetin alfa.

A statistically significant difference in time to first RBC transfusion was observed by the RRC between subjects who had a response to epoetin alfa (median [95% CI]=NE [not evaluable; 17.0, NE] days) and subjects who did not have a response to epoetin alfa (34.5 [24.0, 88.0] days) and all placebo subjects (37.0 [22.0, 64.0] days) at p=0.008. The HR was 0.233 (0.087, 0.624) corresponding to the time to first RBC transfusion for all subjects in the placebo group versus the time to first RBC transfusion for subjects who had a response to epoetin alfa. However, a lesser difference was observed between subjects in the placebo group versus subjects who did not have a response to epoetin alfa (HR = 0.760 (0.454, 1.270) with a p-value of 0.015).

A decrease in the percentage of subjects with transfusions over time through Week 24 was observed in the epoetin alfa group (ie, decrease from 51.8% in 8 weeks prior to baseline to 24.7% of subjects between Week 16 and Week 24); whereas, an increase was observed in the placebo group (ie, increase from 48.9% in 8 weeks prior to baseline to 54.1% of subjects between Week 16 and Week 24).

Improvement of epoietin alfa in quality of life was observed mostly in epoetin alfa responders at Week 24.

Approximately one third of the population continued the treatment up to Week 48, these supportive data confirmed efficacy data in this small population but should be interpreted regarding the safety data in order to avoid an overexposure of the drug.

The 85 subjects of the epoetin alfa group and 45 subjects of the placebo group were included in the safety analysis. Subjects received a starting dose of 450 IU/kg adjusted to a maximum of 1,050 IU/kg once every week. The maximum total dose was 40,000 IU administered once every week (the first 8 weeks of treatment), and 80,000 IU once every week after Week 8. At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase. The safety results included all data from baseline through Week 52 (ie, end-of-study visit after end of treatment extension phase Week 48).

During the first 24 weeks of the study,

Higher percentage of subjects in the placebo group than in epoetin alfa group reported 1 or more treatment-emergent adverse events (88.9% vs. 77.6%).

Similar percentage of subjects reporting at least 1 treatment-emergent adverse event of toxicity grade 3 or grade 4 was similar between the epoetin alfa and placebo groups (25.9% vs. 26.7%).

Higher subjects in the epoetin alfa group (25.9%) than in the placebo group (17.8%) reported treatment-emergent serious adverse events.

Nine (10.6%) subjects in the epoetin alfa group discontinued treatment due to adverse event compared with 6 (13.3%) subjects in the placebo group.

There is no new safety signal. The most common treatment-emergent adverse events during the first 24 weeks that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group were asthenia, fatigue, nasopharyngitis, diarrhea, dyspnea, constipation, and pruritis.

Two treatment-emergent serious adverse events in the epoetin alfa group were considered related to study agent by the investigator in EPOANE 3021 study: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive (after 24 weeks of treatment). PRCA is a very rare adverse event, which is strongly followed for all erythopoeitins. There is no relevant data allowing assuming an increased risk of PRCA in EPO treated MDS.

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the

placebo group experienced disease progression. Among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior to or at Week 24.
After Week 24, 3 additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48).

Safety data evaluation in registry studies were focussed on the impact of EPO alfa on the risk of acutisation in SMD.

In the French registry (without placebo group), the tolerance was good and most patients could receive the totality of the treatment. In this cohort of patients, the risk of acute leukaemia is about 7%, which is aligned with known incidence in IPSS Low or Int-1 risk population. In Italian registry, any statistical difference in leukemic evolution rate in treated versus untreated patients were observed. The authors concluded that no potential leukemic risk could be attributed to EPO alpha therapy. In Spanish registry, patients in this study receiving treatment with ESA did not appear to have a higher incidence of disease progression to AML (13.7% in patients treated with ESAs and 15.8% in RBC transfusion support group). However, the report did not focus the evaluation of disease progression in the 25 patients treated by EPO alfa.

The data registers and prospective studies seemed to be mature enough to ensure patient safety, including the risk of acutisation.

Finally, among the 8 deaths, 4 subjects had cardiac/renal related comorbidities, 3 subjects had MDS disease progression and 1 subject had a sudden death with unclear cause. Due to the low number of deaths in the elderly population, no supplement recommendation could be propose. In the same way that the other indications, a warning in the section 4.2 of the SmPC to physicians "Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a phycians's evaluation of the individual patient's clinical course and condition is necessary".

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Myelodysplastic syndromes are clonal marrow stem-cell disorders, characterized by ineffective hemopoiesis leading to blood cytopenias, and by progression to acute myeloid leukemia (AML) in one third of patients. The natural course of MDS is highly variable, with survival ranging from a few weeks to several years. Anemia is a major contributor to the symptomatology of MDS.

Since transfusion dependence negatively affects survival in patients with MDS, epoetin alfa treatment might reduce or avoid transfusion and ultimately provide a survival benefit. Therefore, the MAH submitted in this procedure the EPOANE 3021 controlled study to evaluate treatment

in this patient population.

Benefits

Beneficial effects

As the primary efficacy endpoint, the percentage of the responders in the epoetin alfa group (n=85) was significantly higher compared with the placebo group (n=45) at any time during the first 24 weeks (31.8% vs. 4.4%; p<0.001). The higher rate of erythroid response in epoetin alfa group than in placebo group was confirmed at Week 24 with the response review committee (RRC).

A difference in erythroid response rate was observed between subjects with baseline serum erythropoietin < 200 mU/mL and those ≥200 mU/mL (31.8% vs 0%). Thus, all of the responding subjects were in the strata with serum erythropoetin less than 200 mU/mL during screening.

Although the response rate in subjects with prior transfusions was less, 7/31 (22.6%) subjects with prior transfusions compared with 20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, (two subjects with prior transfusion reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline).

Higher statistically significant difference in time to first RBC transfusion after Week 4 in the epoetin alfa group compared with the placebo group (median= 142 vs. 50.0 days; p=0.007) has been observed with the HR of 2.029 (1.194, 3.451).
A decrease in the percentage of subjects with transfusions over time through Week 24 was observed in the epoetin alfa group (ie, decrease from 51.8% in 8 weeks prior to baseline to 24.7% of subjects between Week 16 and Week 24); whereas, an increase was observed in the placebo group (ie, increase from 48.9% in 8 weeks prior to baseline to 54.1% of subjects between Week 16 and Week 24).

Improvement of epoietin alfa in quality of life was observed mostly in epoetin alfa responders at Week 24.

Uncertainty in the knowledge about the beneficial effects

The primary efficacy parameter is defined by the demonstration of ER according to IWG 2006 criteria at any time during the first 24 weeks of the study. It is unclear if Hb measurement were based on untransfused patients within the previous week of Hb assessment or any transfusion prior to week 24. However, the RRC has individually re-evaluated the ER of each subject taking into account the stability of the response and exclude Hb measurements considered due to

transfusion. The approach chosen by the MAH seems reasonable.

Due to the small size in patients who have Hb levels less than 8 g/dL at baseline and are already transfusion dependent in EPOANE 3021 study, it is not possible to conclude the benefit of the drug in this subgroup of patients. Basing on these data, the dependence transfusion should not be considered as a restriction in EPREX indication.
As the erythroid response rate was not evidenced in subjects with baseline serum erythropoietin ≥200 mU/mL, the beneficial effect in this population was not demonstrated.

Risks

Unfavourable effects

The 85 subjects of the epoetin alfa group and 45 subjects of the placebo group were included in the safety analysis. Subjects received a starting dose of 450 IU/kg adjusted to a maximum of 1,050 IU/kg once every week. The maximum total dose was 40,000 IU administered once every week (the first 8 weeks of treatment), and 80,000 IU once every week after Week 8. At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase.

During the first 24 weeks of the study,

Higher percentage of subjects in the placebo group than in epoetin alfa group reported 1 or more treatment-emergent adverse events (88.9% vs. 77.6%).

Similar percentage of subjects reporting at least 1 treatment-emergent adverse event of toxicity grade 3 or grade 4 was similar between the epoetin alfa and placebo groups (25.9% vs. 26.7%).

Higher subjects in the epoetin alfa group (25.9%) than in the placebo group (17.8%) reported treatment-emergent serious adverse events.

Nine (10.6%) subjects in the epoetin alfa group discontinued treatment due to adverse event compared with 6 (13.3%) subjects in the placebo group.
There is no new safety signal. The most common treatment-emergent adverse events during the first 24 weeks that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group were asthenia, fatigue, nasopharyngitis, diarrhea, dyspnea, constipation, and pruritis.

Two treatment-emergent serious adverse events in the epoetin alfa group were considered related to study agent by the investigator in EPOANE 3021 study: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive

(after 24 weeks of treatment). PRCA is a very rare adverse event, which is strongly followed for all erythopoeitins. There is no relevant data allowing assuming an increased risk of PRCA in EPO treated MDS.

Uncertainty in the knowledge about the unfavourable effects

During the first 24 weeks, 11 (12.9%) subjects in the epoetin alfa group and 4 (8.9%) in the placebo group experienced disease progression. Among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior to or at Week 24.
After Week 24, 3 additional subjects in the epoetin alfa group experienced disease progression (1 at Week 44 and 2 at Week 48). The MAH also provided registry studies. Safety data evaluation in these supportive studies were focussed on the impact of EPO alfa on the risk of acutisation in SMD. In the French registry, the risk of acute leukaemia is about 7%, which is aligned with known incidence in IPSS Low or Int-1 risk population. In Italian registry, any statistical difference in leukemic evolution rate in treated versus untreated patients were observed. In Spanish registry, patients in this study receiving treatment with ESA did not appear to have a higher incidence of disease progression to AML (13.7% in patients treated with ESAs and 15.8% in RBC transfusion support group). The data registers and prospective studies seemed to be mature enough to ensure patient safety, including the risk of acutisation. Based on these results, at this stage, it seems not necessary to request a PASS to the MAH.

Among the 8 deaths, 4 subjects had cardiac/renal related comorbidities, 3 subjects had MDS disease progression and 1 subject had a sudden death with unclear cause. Due to the low number of deaths in the elderly population, no supplement recommendation could be proposed. In the same way that the other indications, the MAH added a warning in the section 4.2 of the SmPC to physicians "*Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a phycians's evaluation of the individual patient's clinical course and condition is necessary*".

Benefit-Risk Balance

As of June 2016, EPO-alpha has not yet been indicated in the treatment of anaemia in low-or intermediate-1 MDS. However, it has been used for years for this purpose in real-world setting.
As part of the population (IPSS low / intermediate), it does not exist to date therapeutic alternative for EPO. EPOANE 3021 study confirmed the efficacy of EPO alfa on the erythroid response in this population of patient. No new safety signal emerged from the study.

Conclusion

As a conclusion, the B/R Balance of Eprex/Erypo in the treatment of symptomatic anaemia

(haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL) can be considered positive. Overall conclusions were endorsed by NL, DE, DK and IT. As the EPOANE3021 study constitutes a confirmatory clinical trial for the approval of Eprex in this new indication, the Rapporteur agrees to grant a non-cumulative period of one year of data in accordance with the Article 10.5 of Directive 2001/83/EC.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

Major objection:

The results of the study show that a positive outcome is only achieved for patients with serum erythropoietin level at screening <200 mU/mL. The targeted indication does not mention any restriction on the level of serum EPO before starting Eprex to tell apart patients who could benefit from the others.
The MAH should discuss the differential of efficacy observed between patients with serum EPO level at screening >= and < 200 mU/mL, and how in practice it is intended to deal with this issue, since patients with serum erythropoietin level >= 200 mU/mL would be exposed to Eprex associated risks without expecting any beneficial effect.
Very limited safety data are available in patients with serum EPO level > 200 mU/mL. Any benefit/risk assessment might therefore be difficult to draw. Please justify the use of EPREX in this particular population. Data should notably analyzed according to serum erythropoietin levels ≤ or >200 mU/ml.

Other concerns:

Efficacy:

1. The MAH should justify that the proposed indication is not broader than the investigated target population or should be further specified as “treatment of symptomatic anemia associated with primary MDS” (comment).

2. The MAH should discuss whether the special weight based dosing recommendations and resulting major protocol deviations for dosing affected the efficacy and safety of the treatment, in view of 1. higher response rates of the supportive French study or those mentioned e.g. in the ESMO clinical guidelines (Fenaux et al. 2014) and 2. the general recommendation for ESAs to use the lowest effective dose (comment).

3. The prognostic score IPPS[10] was revised from the start of the study (23 June 2011) and its analysis in March 2016 and called IPPS-R. Changes in patient's distribution in this score, in particularly between score IPSS-R intermediate and high have been observed[9]. The interpretation of the data could be modified. In order to clarify the data at the baseline and to confirm epoietin alfa in SMD low and intermediate risk, the MAH could update the distribution of the patients regarding the score IPPS-R.

4. Globally, prior and concomitant therapies used were similar in the two group except use of antithrombotic agents which were higher in the epoetin alfa group and use of glucorticoïds, angiotensin II, vitamin B1 and iron chelating agents in placebo group. The MAH should discuss the higher use of antithrombotic agents regarding the safety evaluation (e.g. higher TVE in epoetin alfa group). Descriptive discrepancies (hypertension, type2 diabetes or dyslipidemia…) should be further discussed in term of possible impact on the treatment outcome (efficacy and safety).

5. There is a high rate of major protocol deviations. According to the MAH, these deviations are mainly due to dosing problems. The MAH should be more specific about the deviations to the dose. The MAH should provide for each group, the number of subjects who received an incorrect starting dose (at baseline) and the number of subjects who received an incorrect dose at any following visit up to week 24.

6. A total of 11.7% of all hemoglobin measurements were done with hemophotometers by the subject or caregiver. The MAH should discuss the reliability of the primary criterion outcome in regards to the heterogeneity of the Hb measurement throughout the subject study participation (hospital lab, local lab, hemophotometer…). The MAH should provide the proportion of subjects for whom the Hb measurement was performed the same way from week 1 to week 24 in both arms.

7. The table "extent of exposure" seems to reflect the total number of doses actually received by subjects through their entire participation in the study. The MAH should also provide for both arms, the number of subjects who actually received 25 doses from day 1 to week 24 (one dose per week as recommended in the SmPC). Moreover, the MAH should provide the distribution of the number of doses received by the responders in the Eprex arm within the first 24 weeks of the study. The same should be provided for the extension phase.

8. In order to characterize the severity of the population and thus to better document the efficacy of epoietin alfa in MDS patients even if concerning a small size population (n=9), the MAH should comment all the erythroid response according to the transfusions need (number of subjects receiving ≤2, >2 ou ≤4 RBC units in 8 weeks).

[10] Greenberg PL et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65.

9. There were 2 events contributing to the overall composite primary endpoint:

a) ≥1.5 g/L Hb increase from baseline
b) Reduction of RBC transfusions of at least 4 units for 8 weeks compared to transfusion performed within the 8 weeks before treatment.

Results for the 2 individual events should be provided by the MAH.
Moreover the MAH should confirm that only RBC transfusion given for a Hb ≤ 9.0 g/dL pre-treatment was counted in the RBC transfusion response evaluation as stated in the 2006-IWG response criteria. Otherwise, a sensitivity analysis of the primary endpoint should be performed, taking into account this condition.

10. Finally, the impact of the RBC transfusions on the Hb change is not clear, a new sensibility analysis is required, the Hb values of >1.5 g/L from baseline after three week of the last RBC transfusion should not be consider as positive erythroid response, the MAH should assess the data again considering only positive Hb response after three week transfusion-free, the clinical relevance of the results obtained from this re-analysis in comparison with the main results of the primary endpoint should be discussed (comments).

11. The OS results of the Italian registry only show an OS benefit for EPO treatment in patients with baseline Hb levels between 8 and 10 g/dL who are not transfusion dependent. Thus, the MAH should discuss the benefit of Eprex treatment for patients who have Hb levels less than 8 g/dL at baseline or are already transfusion dependent (comments).

12. The higher rate of erythroid response in epoetin alfa group than in placebo group was confirmed at Week 24 with both the RRC and investigator evaluation and in both ITTm and PP analysis evaluation. Nevertheless, there are discrepancies between investigators and RRC response evaluations. Disagreements should be detailed and discussed (number of responders versus non responders disagreements and if any, number of disagreements in positive response to treatment: ≥ 1.5 g/L versus < 4 units RBC transfusion).

13. Based on the RRC assessment of responders set at any time during the first 24 weeks in the mITT analysis, subjects in the epoetin alfa group had a higher mean response duration of day than in the placebo group through completion of this 52-week study (192.3 ± 88.92 vs 99.0 ± 69.30 days). Comparing to a published study (Park et al., 2008[11]) evaluating data from French and Belgian hematologic centers of the Groupe Francophone des Myelodysplasies (GFM) with 403 patients, median duration of response from the onset of rHuEPO was 24

[11] Park S et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008 Jan 15;111(2):574-82.

months according to IWG 2006 criteria which is much higher than in this study. The MAH should discuss these observed discrepancies.

Safety

14. In order to clarify the adverse events related to study agent, the MAH should provide a table of all adverse events, precising if the adverse effect is related or not to study agent. Adverse events doubtfully, possibly, probably, very likely related to study agent should be considered as related to study agent.
In addition, frequencies of AEs during the first 24 weeks vs. extension phase should be compared (comment).

15. The MAH should document for all patients presented a TVE the Hb level at the baseline, the delay and the intensity of the response to the drug, the Hb level at the response, the additional risk factor, the concomitant treatment. These informations could lead to any recommendations for the use of EPO alfa in elderly patients with additional risk (e.g. PIL).

16. Eight deaths were observed during the entire study period due to treatment-emergent adverse events (7 in the epoetin alfa group and 1 in the placebo group). None of the deaths were considered related to study agent by the investigators. However, in 5 deaths, investigations revealed that all these cases concerning elderly patients with history of renal insufficiency, of hypertension or cardiovascular pathology. The MAH should further discuss these cases taking into account these comorbidities. As required above, the MAH should propose some recommendations of the use of EPO alfa in elderly patients with comorbidities.

SmPC

17. The MAH should mention in section 5.1 that all of the responding subjects were in the strata with serum erythropoietin less than 200 mU/ml during screening.
In addition, please add for the EPO levels the units as mentioned in the International System of Units (comment).

18. The MAH should justify the (very short) dosing recommendations proposed for section 4.2, which cover only a part of the dosing recommendations used during the study (CSP section 6) and are thus considered insufficient and confusing, and align accordingly (comment).

19. There were 4 (4.7%) subjects in the epoetin alfa group with TVEs (sudden death, ischemic stroke, embolism [distal deep venous thrombosis], and phlebitis [distal deep venous thrombosis]); all TVEs occurred during the first 24 weeks of the study. These higher rate should be mentioned in the section 5.1 of the SmPC.

20. According to the MAH, there is no new safety signal. The most common treatment-emergent adverse events during the first 24 weeks that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group were asthenia, fatigue, nasopharyngitis, diarrhea, dyspnea, constipation, and pruritis. Therefore, SmPC section 4.8 should be updated with new data from pivotal study EPOANE3021, i.e. including information about patients treated for MDS in the introductory paragraph "Of a total 3,262 subjects in 23 randomised,… studies,…" and any further concerned paragraph (comments). In addition, the MAH is requested to adapt the tabular format of undesirable effects as follows:

MedDRA system organ classification (SOC)	Adverse Reaction (Preferred Term Level)	Frequencies

believes that this tabular format is more clear (supported by).

21. The MAH is requested to cite the name and the number of all the studies reporting in the section 5.1. (comment).

22. Section 5.2: In the section upon pediatric population the MAH is requested to specify name and number of the study. Moreover the MAH is requested to clarify if the study in this section is the study. In this case the MAH is request to discuss and clarify the discrepancies in the number of subjects reported in SPC (7 preterms newborn) from that reported in the study itself (8 preterms newborn) (comments).

23. Finally, responses submitted to the Medical products Agency should contain product information also in Word format. Proposed changes should be shown as tracked changes (comment).

VII. ASSESSMENT OF RESPONSES OF THE MAH

MAJOR OBJECTION

The results of the study show that a positive outcome is only achieved for patients with serum erythropoietin level at screening <200 mU/mL. The targeted indication does not mention any restriction on the level of serum EPO before starting Eprex to tell apart patients who could benefit from the others.

The MAH should discuss the differential of efficacy observed between patients with serum EPO level at screening >= and < 200 mU/mL, and how in practice it is intended to deal with this issue, since patients with serum erythropoietin level >= 200 mU/mL would be exposed to Eprex associated risks without expecting any beneficial effect.

Very limited safety data are available in patients with serum EPO level > 200 mU/mL. Any benefit/risk assessment might therefore be difficult to draw. Please justify the use of EPREX in this particular population. Data should notably analyzed according to serum erythropoietin levels ≤ or >200 mU/ml.

APPLICANT RESPONSE

The impact of baseline serum erythropoietin (sEPO) levels on erythroid response (ER) in patients with MDS reported in the literature has been summarized in the literature review (see initial application: Literature review/Sec 4.3.1.1.3 [Mod5.3.5.4]). Baseline sEPO levels were significantly higher in non-responding patients ($p<0.005$) than in responders (Ludwig et al, 1993)[12]. Results of many studies indicated that sEPO level was the most frequently reported significant predictor for response, and proved to be a particularly useful prognostic indicator of treatment success (see initial application: Literature review/Sec 4.3.1.1.3 [Mod5.3.5.4]). Based on the collective information, many MDS guidelines include the sEPO level ≤500 mU/mL as one of the criteria for lower risk MDS patients with symptomatic anemia to receive ESAs as standard therapy (NCCN 2016)[14].

In the EPOANE3021 study, subjects were stratified according to their screening sEPO level (<200 or ≥200 mU/mL). Additional subgroup analyses were performed based on the screening sEPO level (<200 or ≥200 mU/mL), data are provided as attachments with this response document, and results are discussed below.

Subject Disposition Based on Screening Serum Erythropoietin Level (<200 or ≥200 mU/mL)

In the EPOANE3021 study, according to the protocol, only subjects who had a screening sEPO level <500 mU/mL were to be enrolled. The majority of subjects had a screening sEPO level <200 mU/mL: 110 of 130 (84.6%) all subjects, 71 of 85 (83.5%) subjects in the epoetin alfa group and 39 of 45 (86.7%) subjects in the placebo group. Nineteen of 130 (14.6%) subjects in the study who had sEPO ≥200 mU/mL, 13 of 85 (15.3%) subjects in the epoetin alfa group and 6 of 45 (13.3%) subjects in the placebo group. One subject in the epoetin alfa group did not have a sEPO value at screening (Mod5.3.5.1/EPOANE3021 CSR Erratum/Table TSIDS01a).

Impact of Screening Serum Erythropoietin Level (<200 or ≥200 mU/mL) on Primary Efficacy Outcome

For the primary efficacy endpoint in the EPOANE3021 study, erythroid response according to the International Working Group (IWG) 2006 criteria assessed by members of experts in the Response Review Committee (RRC), all 27 responding subjects in the epoetin alfa group had screening sEPO <200 mU/mL, and there were no responders in subjects with screening sEPO ≥200 mU/mL (see initial application: CSR

EPOANE3021/Sec 6.2 [Mod5.3.5.1]). Therefore, to more accurately reflect the results of EPOANE3021 study in the labeling, the Applicant has added the restriction of sEPO <200 mU/mL to the proposed new indication (see Mod1.3.1/SmPC).

The proposed revised indication is as follows (in "track changes" mode: addition marked as double underline):

> *EPREX, ERYPO is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).*

Safety Analyses for Subjects with Screening Serum Erythropoietin Level (<200 or ≥200 mU/mL)

To further address any potential safety concerns of using epoetin alfa in patients with sEPO ≥200 mU/mL, the Applicant also conducted a series of post hoc analyses focusing on the safety profile of the 19 subjects with the screening sEPO ≥200 mU/mL in the EPOANE3021 study. The list of post hoc safety analyses is shown below and the analyses results are provided in the attachments:

- Treatment-emergent adverse events (TEAEs) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFAE01d) and screening sEPO ≥200 mU/mL (Attachment TSFAE01e),
- Treatment-emergent serious adverse events (TESAEs) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFAE03d) and screening sEPO ≥200 mU/mL (Attachment TSFAE03e),
- Treatment-emergent adverse events (TEAEs) of toxicity grade 3 or 4 that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFAE04d) and screening sEPO ≥200 mU/mL (Attachment TSFAE04e),
- Treatment-emergent adverse events (TEAEs) leading to permanent discontinuation of study treatment that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFAE05d) and screening sEPO ≥200 mU/mL (Attachment TSFAE05e),
- Treatment-emergent adverse events (TEAEs) leading to deaths (outcome = fatal) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFAE09d) and screening sEPO ≥200 mU/mL (Attachment TSFAE09e),
- Treatment-emergent adverse events (TEAEs) (in ≥5% of the subject) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (see initial application: CSR EPOANE3021/Att TSFAE12a [Mod5.3.5.1]), and re-supplied in

this response document for convenience of review: Attachment TSFAE12a) and screening sEPO ≥200 mU/mL (Attachment TSFAE11b),

- Disease progression that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (see initial application: CSR EPOANE3021/Att TSFREL02 [Mod5.3.5.1]), and re-supplied in this response document for convenience of review: Attachment TSFREL02) and screening sEPO ≥200 mU/mL (Attachment TSFREL02a)
- Disease progression to acute myeloid leukemia (AML) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFREL03a) and screening sEPO ≥200 mU/mL (Attachment TSFREL03b).
- Thrombotic vascular events (TVEs) that occurred in first 24 weeks for subjects with screening sEPO <200 mU/mL (Attachment TSFTVE02) and screening sEPO ≥200 mU/mL (Attachment TSFTVE02a).

Summary of Safety Analyses Results and Discussion

A summary of key safety findings for the first 24 weeks in each sEPO subgroup and in the total study subjects is provided in the Table 1 below. Since there were no subjects with screening sEPO ≥200 mU/mL who continued to the extension phase of the study, the comparison of safety profile between subjects with screening sEPO <200 mU/mL and ≥200 mU/mL was performed only for the first 24 weeks of the study.

Table 1: Summary of Key Safety Findings for the First 24 Weeks in Total Study Population and in Subgroups Based on Subjects' Screening Serum Erythropoietin Levels in the EPOANE3021 Study

	Serum Erythropoietin <200 mU/mL		Serum Erythropoietin ≥200 mU/mL		Total	
	Placebo (n=39)	Epoetin Alfa* (n=71)	Placebo (n=6)	Epoetin Alfa* (n=13)	Placebo (n=45)	Epoetin Alfa (n=85)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Subjects with AE	34 (87.2)	55 (77.5)	6 (100.0)	11 (84.6)	40 (88.9)	66 (77.6)
Subjects with SAE	7 (17.9)	19 (26.8)	1 (16.7)	3 (23.1)	8 (17.8)	22 (25.9)
Subjects with Grade 3 or 4 AE	9 (23.1)	19 (26.8)	3 (50.0)	3 (23.1)	12 (26.7)	22 (25.9)
AE leading to treatment DC	5 (12.8)	7 (9.9)	1 (16.7)	2 (15.4)	6 (13.3)	9 (10.6)
AE with fatal outcome	1 (2.6)	4 (5.6)	0	0	1 (2.2)	4 (4.7)
Disease progression	3 (7.7)	8 (11.3)	1 (16.7)	3 (23.1)	4 (8.9)	11 (12.9)
Progression to AML	2 (5.1)	3 (4.2)	0	0	2 (4.4)	3 (3.5)

TVE	0	3 (4.2)	0	1 (7.7)	0	4 (4.7)

AE = adverse event; AML = acute myeloid leukemia; DC = discontinuation; SAE = serious adverse event; TVE= thrombotic vascular event.
*: One subject in the epoetin alfa group did not have a sEPO value at screening.
source: Attachments TSFAE01d and e, TSFAE03d and e, TSFAE04d and e, TSFAE05d and e, TSFAE09d and e, TSFAE11b, TSFREL03a and b, TSFTVE02 and 02a; Initial application: CSR EPOANE3021/Table 17 and Att TSFAE12a (Mod5.3.5.1).

Overall, as shown in the Table 1, the results of subgroup analyses showed that the key safety findings in the subjects with sEPO level ≥200 mU/mL were generally consistent with that in subjects with sEPO level <200 mU/mL, except that the adverse events of fatal AEs and progression to AML occurred only in the group of sEPO <200 mU/mL. Since only a small number of subjects in the EPOANE3021 study (a total of 19 subjects: 13 subjects in the epoetin alfa group and 6 subjects in the placebo group) had sEPO level ≥200 mU/mL, it is difficult to draw a conclusion on safety based on these limited safety data in MDS patients with sEPO level ≥200 mU/mL from this study.

In the literature, it has been reported that sEPO level correlated with survival. In a report by Wallvik et al (2002)[21], the differences in survival appeared to be significant only at the cut-off sEPO levels less than 100 U/L, and for patients with sEPO ≤200 U/L and >200 U/L, the difference in median survival was not statistically significant (28 vs 25 months, p=0.341)[21]. Greenberg et al (2009)[4] reported in a univariate analysis of overall survival that the subgroup with sEPO <200 mU/mL had a hazard ratio (HR) of 0.71 (95% CI: 0.39-1.28) and the subgroup with sEPO ≥200 mU/mL had a HR of 0.87 (95% CI: 0.37-2.02), and the difference was not statistically significant.

In summary, use of epoetin alfa in patients with a screening sEPO ≥200 mU/mL in the EPOANE3021 study did not cause any additional harm to or raise any new safety issues in this patient population. The general safety profile of epoetin alfa remains the same. However, because the number of subjects with a screening sEPO ≥200 mU/mL in the EPOANE3021 study was too small to draw a safety conclusion, and more importantly, because there was no additional benefit in the primary efficacy measures for this subgroup, the Applicant proposes to add the sEPO <200 mU/mL restriction in the new indication for the revised label.

Assessor's comment

The number of subjects with a screening sEPO ≥200 mU/mL in the EPOANE3021 study was too small to draw a safety conclusion (19 of 130 (14.6%) subjects in the study, 13 of 85 (15.3%) subjects in the epoetin alfa group and 6 of 45 (13.3%) subjects in the placebo group). However, this study failed to demonstrate additional benefit in the primary efficacy measures for this subgroup. Thus, the RMS agrees with the MAH that it is necessary to add the sEPO <200 mU/mL restriction in the new indication in order to avoid exposure of any refractory population.

Issue solved

OTHER CONCERNS

EFFICACY

QUESTION-1

The MAH should justify that the proposed indication is not broader than the investigated target population or should be further specified as "treatment of symptomatic anemia associated with primary MDS".

APPLICANT RESPONSE

The Applicant has revised the proposed indication in the product label to the following (in "track changes" mode: addition marked as double underline) (see Mod1.3.1/SmPC).

EPREX, ERYPO is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

The rationale for addition of the sEPO <200 mU/mL restriction in the proposed indication is provided above in the response to the major objection.

Assessor's comment

The RMS agrees with the new indication proposed by the MAH.

Issue solved.

QUESTION-2

The MAH should discuss whether the special weight based dosing recommendations and resulting major protocol deviations for dosing affected the efficacy and safety of the treatment, in view of 1. higher response rates of the supportive French study or those mentioned e.g. in the ESMO clinical guidelines (Fenaux et al. 2014) and 2. the general recommendation for ESAs to use the lowest effective dose.

APPLICANT RESPONSE

The background information and the reasons for using a weight-based regimen of epoetin alfa in the EPOANE3021 study have been discussed in detail in the protocol (see initial application:

CSR EPOANE3021/App-1 [Mod5.3.5.1]), the CSR (see initial application: CSR EPOANE3021 [Mod5.3.5.1]), and the clinical overview (see initial application: Clinical Overview [Mod2.5]).

The impact of weight-based dosing used in the EPOANE3021 study, the resulting major protocol deviations, and the impact of these dosing-related major protocol deviations on the study results were also discussed in the CSR (see initial application: CSR EPOANE3021/Sec4.4 [Mod5.3.5.1]) and the clinical overview (see initial application: Clinical overview/Sec 4.1.4 [Mod2.5]).

The differences in posology including dosing regimens and implication on study results comparison between the EPOANE3021 study and the supporting MDS registry studies (including the French MDS registry study) were discussed in the clinical overview (see initial application: Clinical Overview/Sec4.1.2.3 [Mod2.5]).

The major benefit risk profiles of epoetin alfa, including the dosing regimen, efficacy and safety results, in the EPOANE3021 study, the 3 supportive MDS registry studies (including the French MDS Registry study), and those reported in the literature for similar patient population, were summarized side by side in the clinical overview (see initial application: Clinical Overview/Table 8 [Mod2.5]).

To focus on the Agencies' comment and request, the key dosing regimen and efficacy measures in the EPOANE3021 study, the supportive French MDS Registry study and in the European Society for Medical Oncology (ESMO) clinical guidelines (Fenaux et al, 2014)[2] are provided in the Table 2.

Table 2: Comparison of Dosing Regimen and Erythroid Response Rate

	EPOANE3021	**French MDS Registry**	**ESMO Guidelines** (Fenaux et al, 2014)[2]
Dosing regimen	-weight-based dosing regimen -generally treated with a lower starting dose, and gradually stepwise titrated up until obtaining a response	fixed dosing regimen	fixed dosing regimen
Weekly dose	337.5 to 1050 IU/kg (10k to 80k IU)	40k IU (for 70.4% of the patients) (4,000-80,000 IU)	30,000 to 80,000 IU
Study treatment and follow-up	up to 52 weeks	76.7 months (EPREX)	N/A
Erythroid response rate	31.8% [4.4% placebo, p<0.001] (IWG2006 by RRC) 45.9% (benefited, determined by RRC) 50% (Strata 1: sEPO <200 mU/mL and no transfusion)	58% (EPREX as first line)	~60% when the baseline sEPO level is low and transfusion requirement is absent or limited

ESMO = European Society for Medical Oncology; IWG = International Working Group; MDS = myelodysplastic syndromes; N/A = non-applicable; RRC = Response Review Committee; sEPO = serum erythropoietin.

Source: Initial application: CSR EPOANE3021 (Mod5.3.5.1); Mod5.3.5.1/EPOANE3021 CSR Erratum; Initial application: French registry report (Mod5.3.5.4); Fenaux et al, (2014)[2]

In the EPOANE3021 study, weight-based dosing was used, with the aim of administering the lowest effective dose to each subject. Although a randomized, multicenter study revealed no difference in effectiveness, safety, and quality-of-life benefits of epoetin alfa in anemic cancer patients on platinum-based chemotherapy between fixed dosing (10,000 IU) and weight-adjusted dosing (150 IU/kg)[12], a similarly designed study has not been conducted in patients with MDS. For safety purposes, subjects in the EPOANE3021 study were treated with a weight-based dosing regimen, initiated with a lower starting dose and gradually titrated up stepwise until a response was obtained.

In addition to the weight-based vs. fixed dosing regimen difference between the EPOANE3021 study and the French MDS Registry study, there were additional factors in the EPOANE3021 study that had direct impact on dosing: ie, the weekly hemoglobin (Hb) measurements and the predefined stringent dose adjustment rules. These measures were designed primarily for safety purposes to limit the risk of excessive Hb response. However, it has been noted that application of these conditions (such as dose hold and dose reductions) in the EPOANE3021 study also led to an increased incidence of drug interruption and discontinuation, which resulted in major protocol deviations. For example, with respect of dosing related protocol deviations in the epoetin alfa group, there were approximately twice as many subjects who received a lower dose of study drug (20%) than those who received a higher dose of study drug (10.6%) (see initial application: CSR EPOANE3021/Table 9 [Mod5.3.5.1]). In addition, incidences of missing dose or reducing dose not according to the protocol could also have negatively impacted the response rate. Since some subjects responded only to a higher dose of epoetin alfa, and they failed to respond or lost response following drug interruption and/or dose reduction, therefore, it is plausible to speculate that drug interruption and discontinuation would have a negative impact on the "absolute value" of the erythroid response rate in the EPOANE3021 study, when compared to the response rate reported in the French MDS Registry study or that mentioned in the EMSO guidelines[2].

Nevertheless, despite the apparently lower "absolute" value, the erythroid response rate in the EPOANE3021 study showed a statistically significant difference between the epoetin alfa group and the placebo group. Moreover, when focusing on the strata with no transfusion requirements and sEPO <200 mU/mL in the EPOANE3021 study, an erythroid response rate of 50% (20 of 40

[12] Granetto C, Ricci S, Martoni A, et al. Comparing the efficacy and safety of fixed versus weight-based dosing of epoetin alpha in anemic cancer patients receiving platinum-based chemotherapy. Oncol Rep. 2003;10:1289–1296.

subjects) was observed in the epoetin alfa group (Table 15, and Mod5.3.5.1/EPOANE3021 CSR Erratum). Therefore, the overall erythroid response data in the EPOANE3021 study are consistent with those reported in the French MDS registry study (58%) and those mentioned in the ESMO clinical guidelines (~60%) (Fenaux et al, 2014)[13].The recommendation to use the lowest effective dose is applicable to any drug. However, in the EPOANE3021 study, stringent rules for stopping and reducing the dose were applied: study agent was to be withheld when the Hb concentration exceeded 12 g/dL and not resumed until it dropped below 11 g/dL, regardless of the achievement of erythroid response. If dosing needed to re-start, it had to re-start at a lower dose. These rules were primarily designed for safety purposes. From the efficacy perspective, these conditions have been noted to cause greater fluctuation in the Hb level of affected subjects, and in some cases led to the loss of response or inability to maintain a response for 8 weeks as required by IWG2006 criteria.

Assessor's comment

The weight-based dosing in the EPOANE3021 study was chosed for safety purposes in the EPOANE3021 study. The use of the lowest effective dose with an increasing dose, based on the hemoglobin level is recommended. This is also the regimen used in other indications in the SmPC of the product.

Issue solved.

QUESTION-3

The prognostic score IPPS[14] was revised from the start of the study (23 June 2011) and its analysis in March 2016 and called IPPS-R. Changes in patient's distribution in this score, in particularly between score IPSS-R intermediate and high have been observed. The interpretation of the data could be modified. In order to clarify the data at the baseline and to confirm epoietin alfa in SMD low and intermediate risk, the MAH could update the distribution of the patients regarding the score IPPS-R.

APPLICANT RESPONSE

The EPOANE3021 study was developed in consultation with the ANSM, including the study design features and the International Prognostic Scoring System (IPSS) scoring system. The study was initiated on 29 September 2011.

The revised IPSS (IPSS-R) article was submitted to the Journal Blood on 28 March, 2012, accepted on 17 June 2012, and published on 20 September 2012 (Greenberg 2012). It was

[13] Fenaux P, Haase D, Sanz GF et al. on behalf of the ESMO Guidelines Working Group: Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology; 2014;25(Supp 3);iii57-69.
[14] Greenberg PL et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012 Sep 20;120(12):2454-65.

published approximately one year after the initiation of the EPOANE3021 study. At the time, approximately 41 of 130 (32%) subjects were already enrolled in the EPOANE3021 study. Therefore, to maintain consistency in the study subject population, the IPSS-R scoring system was not adopted. In addition, the neutrophil data count and exact cytogenetic abnormality were not captured in the database, which made it infeasible to conduct a post hoc, retrospective re-classification of study subjects according to the IPSS-R score.

Traditionally, the IPSS scoring system places a higher score based on bone marrow blast percentage and subdivides MDS patients into 4 risk categories (low, int-1, int-2, high). They are further grouped into the "lower-risk" MDS (low and int-1), where correction of cytopenia was the main objective, and the "higher-risk" MDS (int-2 and high), where the reduction or delay of progression or AML evolution and prolonged survival was the objective.

The IPSS-R scoring system was validated more recently by a different research group with the objective of reclassifying patients according to their risk of progressing to AML and providing treatment strategies. The IPSS-R system places a higher score based on patient's cytogenetic abnormality and subdivides MDS patients into 5 risk categories (very low, low, int, high, very high). Using the IPSS-R system, one-quarter of "lower-risk" MDS per classical IPSS were re-classified as having a higher risk, and may potentially require more intensive treatment, while on the other hand, a substantial subset of "higher-risk" MDS patients per classical IPSS were re-classified as lower risk suggesting that IPSS-R can refine the scoring of an individual MDS patient. Nevertheless, it is still a subject of controversy as to how this score can be used to guide the treatment of MDS patients since currently available and licensed drugs have been developed based on the conventional IPSS scoring system (Platzbecker and Fenaux 2015)[15].

In summary, the Applicant believes, that classification of the subjects in the EPOANE3021 study based on the IPSS scoring system, rather than the subsequent IPSS-R system, should not have a substantial impact on establishing whether or not epoetin alfa is efficacious and safe to use in patients with lower risk MDS. The results of the EPOANE3021 study, including data on major predictors of response such as sEPO level and transfusion requirement, provide useful and sufficient information to help physicians assessing the benefit and risk with epoetin alfa therapy in patients with low- or intermediate-1-risk MDS.

Assessor's comment The Rapporteur agrees with the MAH that the scoring change has no impact on efficacy and safety assessment of EPREX in EPOANE3021 study.

Issue solved

[15] Platzbecker U, Fenaux P. Personalized medicine in myelodysplastic syndromes: wishful thinking or already clinical reality? Haematologica. 2015;100(5):568-571.

QUESTION-4

Globally, prior and concomitant therapies used were similar in the two group except use of antithrombotic agents which were higher in the epoetin alfa group and use of glucorticoïds, angiotensin II, vitamin B1 and iron chelating agents in placebo group. The MAH should discuss the higher use of antithrombotic agents regarding the safety evaluation (e.g. higher TVE in epoetin alfa group). Descriptive discrepancies (hypertension, type2 diabetes or dyslipidemia…) should be further discussed in term of possible impact on the treatment outcome (efficacy and safety).

APPLICANT RESPONSE

In the EPOANE3021 study, the percentage of subjects who used anti-thrombotic agents was higher in the epoetin alfa group (47%) than in the placebo group (29%) (see initial application: CSR EPOANE3021/Table 7 [Mod5.3.5.1]). Medical history revealed that the percentage of subjects with a history of cardiovascular or thrombotic events randomized in the epoetin alfa group was also higher than that in the placebo group: eg, atrial fibrillation (8.2% vs. 2.2%), coronary artery disease (7.1% vs. 4.4%), myocardial ischemia (4.7% vs. 0) (see initial application: CSR EPOANE3021/Att TSIMH01[Mod5.3.5.1]). Thus, the imbalance observed in the use of anti-thrombotic agents between 2 treatment groups likely reflected the therapy used for treating "preexisting" disease or preventing the recurrence of these events in these subjects. In addition, a higher rate of TVE was reported in the epoetin alfa group (4 of 85 subjects) in comparison with the placebo group (0 of 45 subjects), although among them, there was only 1 subject with treatment-emergent confirmed TVE, who had no pre-existing conditions predisposing to thrombosis, and was a responder at the time of the TVE event. The remaining 3 subjects were all non-responders. Two of 3 subjects had relevant medical histories and comorbidities: one subject received only 1 dose of epoetin alfa in the EPOANE3021 study, and the other subject had an accidental TVE finding during a CT scan, which was not clear if the TVE incident occurred during the study or before the study. The 3rd subject's TVE was suspected, but never confirmed. For details, please see CSR (see initial application: CSR EPOANE3021/Sec7.2.2.4.1 [Mod5.3.5.1]) and also see response to Question-15 in this document.

The differences in distribution of other concomitant medications between treatment groups were generally consistent with the differences in distribution of comorbidities between the treatment groups. For example, there was a higher percentage of subjects with a history of hypertension in the placebo group than in the epoetin alfa group (62.2% vs. 49.4%) (see initial application: CSR EPOANE3021/Att TSIMH01 [Mod5.3.5.1]). This corresponded to a higher percentage of subjects using angiotensin II antagonists in the placebo group than the epoetin alfa group (33.3% vs. 14.1%) (see initial application: CSR EPOANE3021/Att TSICM02 [Mod5.3.5.1]). There was a higher percentage of subjects with a medical history of diabetes or hyperlipidemia in the epoetin alfa group

than in the placebo group: eg, diabetes mellitus (17.6% vs. 6.7%), hyperlipidemia (2.4% vs. 0) (see initial application: CSR EPOANE3021/Att TSIMH01 [Mod5.3.5.1]). This corresponded to a higher percentage of subjects in the epoetin alfa group than those in the placebo group who used antidiabetic therapies and lipid modifying agents (see initial application: CSR EPOANE3021/Att TSICM02 [Mod5.3.5.1]).

In summary, the differences in the distribution of prior or concomitant medications used between treatment groups in the EPOANE3021 study were generally consistent with the differences in distribution of baseline comorbidities shown in medical history between the treatment groups. The potential impact of the differences in distribution of cardiovascular events in medical history and the use of anti-thrombotic agents between the treatment groups on the incidence of TVE in the EPOANE3021 study has been discussed above and in the Applicant's response to Question-15. Other comorbidities identified to be independently associated with the risk of non-leukemic death are discussed in the Applicant's response to Question-16 in this document.

Assessor's comment

Impact of cardiovascular events in medical history and use of anti-thrombotic agents between the treatment groups on the incidence of TVE has been discussed in Question-15. Other comorbidities identified to be independently associated with the risk of non-leukemic death are discussed in Question-16.

Issue solved

QUESTION-5

There is a high rate of major protocol deviations. According to the MAH, these deviations are mainly due to dosing problems. The applicant should be more specific about the deviations to the dose. The Applicant should provide for each group, the number of subjects who received an incorrect starting dose (at baseline) and the number of subjects who received an incorrect dose at any following visit up to week 24.

APPLICANT RESPONSE

The distribution of subjects who received an incorrect dose is provided in the CSR (See initial application: CSR EPOANE3021/Att TSIPRD02 [Mod5.3.5.1]).

For the convenience of the reviewers, it is copied below as Table 3:

Table 3: Distribution of Subjects who Received an Incorrect Dose

Dosing MPDs Table

	45		85	
	Placebo	%	EPO	%
Received the wrong treatment or incorrect dose	16	35.6%	40	47.1%
Dose was not withheld as mandated by protocol	*1*	*2.2%*	*6*	*7.1%*
IMP withheld earlier than allowed by protocol due to safety concerns (patient that had TVE)	*0*	*0.0%*	*1*	*1.2%*
*Incorrect dose management - lower dose received**	*10*	*22.2%*	*17*	*20.0%*
*incorrect dose management higher dose received***	*1*	*2.2%*	*9*	*10.6%*
Less than 5 days between the injections	*0*	*0.0%*	*2*	*2.4%*
Missed injection	*5*	*11.1%*	*13*	*15.3%*
Received dose more than 1050 IU/KG	*0*	*0.0%*	*1*	*1.2%*
Received more than 450IIU/KG in the first 8 weeks	*0*	*0.0%*	*1*	*1.2%*
Received medication damaged due to temperature excursion	*2*	*4.4%*	*0*	*0.0%*
Received placebo instead of EPO	*0*	*0.0%*	*2*	*2.4%*
Received unassigned kit but it was from the same arm	*0*	*0.0%*	*2*	*2.4%*

*lower dose refers to lower with one or two dosing steps compared to the dose that should have been administered by protocol
** higher dose refers to higher with one or two dosing steps compared to the dose that should have been administered by protocol

Source: Initial application: CSR EPOANE3021/Att TSIPRD02 (Mod5.3.5.1)

In the EPOANE3021 study, 2 subjects received an incorrect dose at baseline, one in each treatment group. One subject ( ) in the epoetin alfa group had a higher dosing level at baseline and Week 1 visit, and one subject ( ) in the placebo group did not receive a dose at baseline visit. Dosing for this subject started at Week 1.

Assessor's comment

There is a high rate of deviation to the dose affecting both groups, a little bit higher in patients treated with the EPO-alpha. However, the per-protocol analysis excluding patients with major deviations to protocol, among which deviation to the dose, confirms the improved response rate when treated by EPO-alpha compared to placebo, showing that these deviations do not significantly alter the overall response to treatments.

Issue solved

QUESTION-6

A total of 11.7% of all hemoglobin measurements were done with hemophotometers by the subject or caregiver. The MAH should discuss the reliability of the primary criterion outcome in regards to the heterogeneity of the Hb measurement throughout the subject

study participation (hospital lab, local lab, hemophotometer…). The Applicant should provide the proportion of subjects for whom the Hb measurement was performed the same way from week 1 to week 24 in both arms.

APPLICANT RESPONSE

In the EPOANE3021 study, several laboratories were used to collect data. A majority of them were used for the purpose of monitoring the safety of study participants. For example, PPD Central Laboratory was used for antibody testing and the hemophotometer was used for Hb level safety monitoring, particularly for elderly subjects who had difficulties to make frequent laboratory visit.

During the EPOANE3021 study, study site laboratories were used for tests performed at subjects' baseline visits and at their monthly site visits for efficacy and safety assessments as well as for study drug dispensing. The investigators used the Hb measurements by site laboratories for the efficacy ER assessment. Between the monthly visits, the subjects were also allowed to monitor their Hb levels at laboratories near to where they live. These "external" laboratories are all certified, but due to equipment differences their results could have been slightly different from those obtained from the site laboratories. The use of "external" laboratories and the hemophotometers for a more frequent Hb measurement aimed for safety monitoring was in accordance with the protocol which was approved by the authorities in all participating countries.

Because of above described situation, it was not unexpected that the proportion of subjects in the EPOANE3021 study who had Hb measured at the same laboratory from screening visit through Week 24 was approximately 50% (44.7% [38 of 85] subjects in the epoetin alfa group, and 53.3% [24 of 45] subjects in the placebo group) (Attachment Table TSFLAB03). However, the Applicant believes that the primary efficacy outcome assessment in the EPOANE3021 study was not significantly affected by the heterogeneity in Hb measurements based on the following facts and considerations.

During the RRC review, the sources of Hb values were clearly indicated. Hb levels measured by hemophotometer were flagged. If there was a noticeable fluctuation between a hemophotometer measurement and the site laboratory value, the measurement from the hemophotometer was disregarded. The expert members of the RRC were fully aware of the potential variations in the hemophotometer measurement, as well as the variations in Hb measurement between various laboratories (as evidenced on the recordings from the RRC meetings). They thoroughly and carefully considered the potential impact of these factors on the Hb measurement during their assessment of the primary efficacy endpoint. For example, in the report by the RRC, one subject ( ) was assessed as not evaluable due to the lack of reliable measurements for a long period, since this subject was not able to visit the site and had a prolonged use of hemophotometer. The RRC assessment of the primary efficacy outcome, erythroid response

according to the IWG2006 criteria was mainly based on the Hb measurements performed by the site laboratories.

In summary, although largely due to safety reasons, some heterogeneity in Hb measurements existed during the EPOANE3021 study, assessment of the primary efficacy endpoint by the RRC according to the IWG2006 criteria was predominantly based on the Hb values from the site laboratory tests, not by hemophotometers. Therefore, the primary efficacy outcome results of the EPOANE3021 study are valid and reliable.

Assessor's comment

The MAH provided the requested information, indicating that roughly half of subjects had, from screening to end of participation (w24), homogeneous Hb measurements collection (i.e. coming from the same lab site). However, the applicant should provide additional data in support of their statement that the primary outcome was not affected by the heterogeneity in Hb measurements. Responder rates should be presented for patients for which the Hb measurement was performed in the same way throughout the 24 weeks and for those with varying Hb collections (hospital lab, local lab, hemophotometer, etc.). Any discrepancies and their impact on the primary efficacy outcomes should be discussed (comment; see below).

Issue partially solved

QUESTION-7

The table "extent of exposure" seems to reflect the total number of doses actually received by subjects through their entire participation in the study. The MAH should also provide for both arms, the number of subjects who actually received 25 doses from day 1 to week 24 (one dose per week as recommended in the SmPC). Moreover, the MAH should provide the distribution of the number of doses received by the responders in the Eprex arm within the first 24 weeks of the study. The same should be provided for the extension phase.

APPLICANT RESPONSE

The dosing distribution and the number of subjects who actually received 25 doses from Day 1 to Week 24 in both treatment groups in the EPOANE3021 study is provided in Table 4.

Table 4: Exposure for First 24 Weeks; Safety Analysis Set (Study EPOANE3021)

	Placebo	Epoetin Alfa
Analysis set: safety	45	85
Number of weekly doses, n (%)		
1	0	2 (2.4%)
5	1 (2.2%)	1 (1.2%)

6	1 (2.2%)	0
7	2 (4.4%)	1 (1.2%)
9	1 (2.2%)	3 (3.5%)
10	0	2 (2.4%)
11	0	1 (1.2%)
12	0	2 (2.4%)
13	1 (2.2%)	2 (2.4%)
14	1 (2.2%)	0
15	1 (2.2%)	0
16	1 (2.2%)	2 (2.4%)
17	1 (2.2%)	4 (4.7%)
18	0	5 (5.9%)
19	1 (2.2%)	0
20	0	2 (2.4%)
21	0	2 (2.4%)
22	1 (2.2%)	7 (8.2%)
23	1 (2.2%)	5 (5.9%)
24	7 (15.6%)	7 (8.2%)
25	25 (55.6%)	37 (43.5%)

Source: TSIEXP01c

Approximately 50% of subjects in the study received 25 doses from Day 1 to Week 24 (a total of 62 of 130 [47.7%] subjects in the study, 37 of 85 [43.5%] subjects in the epoetin alfa group and 25 of 45 [55.6%] subjects in the placebo group) (Table 4).

The dosing distribution and the number of subjects who had exposure after Week 24 through Week 48 in both treatment groups in the EPOANE3021 study is provided in Attachment Table TSIEXP01d. For this period, 6 subjects in the epoetin alfa group and none in the placebo group received 24 doses.

The distribution of the number of doses received by the responders in both treatment groups for the first 24 weeks of the study is provided in Table 5. Ten of the 27 subjects with erythroid response in the epoetin alfa group and 1 of the 2 responders in the placebo group received 25 doses.

The distribution of the number of doses received by the responders in both treatment groups for the extension phase of the study (Week 24 to Week 48) is provided in Table 6.

Table 5: Exposure for First 24 Weeks for Subjects with Erythroid Response at any time during the first 24 Weeks Modified Intent-to-Treat Analysis Set (Study EPOANE3021)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Number of weekly doses, n (%)		
5	0	1 (1.2%)
9	0	1 (1.2%)
10	0	1 (1.2%)

13	0	1 (1.2%)
14	1 (2.2%)	0
16	0	1 (1.2%)
17	0	1 (1.2%)
18	0	4 (4.7%)
20	0	1 (1.2%)
22	0	4 (4.7%)
23	0	1 (1.2%)
24	0	1 (1.2%)
25	1 (2.2%)	10 (11.8%)

Source: TSIEXP01e

Table 6: Exposure for Week 24 to Week 48 for Subjects with Erythroid Response at any time during the first 24 Weeks; Modified Intent-to-Treat Analysis Set (Study EPOANE3021)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Number of weekly doses, n (%)		
1	0	2 (2.4%)
3	1 (2.2%)	0
5	0	1 (1.2%)
7	0	1 (1.2%)
9	0	1 (1.2%)
10	0	1 (1.2%)
14	0	1 (1.2%)
15	0	1 (1.2%)
16	0	1 (1.2%)
18	0	2 (2.4%)
19	0	5 (5.9%)
20	0	1 (1.2%)
21	0	3 (3.5%)
22	0	3 (3.5%)
23	0	1 (1.2%)
24	0	2 (2.4%)

Source: TSIEXP01f

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Assessor's comment

These data show that subjects with erythroid reponse according to the IWG 2006 criteria at any time during the first 24 weeks and after the 24 to the 48 weeks did not necessarily received all the weekly doses. Finally, this could be explained by the fact that dose adjustments were made to maintain hemoglobin concentrations within the target range of 10 g/dl to 12 g/dl. As described in the protocol and reflected in the SmPC, treatment was withheld when the haemoglobin concentration exceeds 12g/dl and then could be restarted once the haemoglobin level is <11 g/dl.

Issue solved

QUESTION-8

In order to characterize the severity of the population and thus to better document the efficacy of epoietin alfa in MDS patients even if concerning a small size population (n=9), the MAH should comment all the erythroid response according to the transfusions need (number of subjects receiving ≤2, >2 ou ≤4 RBC units in 8 weeks).

APPLICANT RESPONSE

In the EPOANE3021 study, there was a total of 29 responders (27 in the epoetin alfa group and 2 in the placebo group) during the first 24 weeks according to the IWG2006 criteria assessed by the RRC.

The distribution of all responders based on their baseline transfusion needs (during the 8 weeks prior to randomization/baseline) is summarized in Table 7.

Table 7: Distribution of Erythroid Responders at Any Time During the First 24 Weeks According to Subjects' Baseline Transfusion Needs (Study EPOANE3021: Modified Intent-to-Treat Analysis Set)

Transfusion in Responders	Placebo (n=45)	Epoetin Alfa (N=85)
Total Responders	2 (4.4%)	27 (31.8%)
Responders with Transfusion Needs (8 weeks prior to randomization / baseline) (Units / 8 weeks)		
0	1	20
1	0	1
2	0	4
3	1	0
4	0	2

Source: Revised CSR Table TEFER01d (Mod5.3.5.1/EPOANE3021 CSR Erratum); Table 8 in this Section of the response document.

In the epoetin alfa group, the majority of the responders (20 of 27 [74%] subjects) had no transfusions during the 8 weeks prior to randomization/baseline. Only 7 subjects in the epoetin alfa group required blood transfusion during the 8-week period prior to randomization/baseline. Due to the small numbers of responders requiring transfusion, it is difficult to draw a definitive conclusion.

Additionally, individual information for responders in the EPOANE3021 study who required a transfusion prior to baseline is listed in the Table 8 below.

Table 8: **Subjects with Erythroid Response who Required Transfusion Prior to Baseline**

Responders (Subject ID)	Treatment Group	Transfusion Needs 8 Weeks Prior to Baseline (units/8weeks)	Screening Serum Erythropoietin (mU/mL)
	epoetin alfa	1	80.8
	epoetin alfa	2	60.0
	epoetin alfa	2	31.0
	epoetin alfa	2	89.1
	epoetin alfa	2	20.8
	epoetin alfa	4	26.0
	epoetin alfa	4	111.0
	placebo	3	28.0
Source: EPOANE3021 Study Database Excel Files: EPOANE3021_Transfusions blinded phase; EPOANE3021_Treatment unblinding codes; EPOANE3021_Serum Erythropoetin on screening randomized subjects; EPOANE3021_Change in subject stratum when using CRF data for stratification;EPOANE3021_RRC report core phase.			

Please note that following issuance of the final CSR, it became evident that the transfusion requirement data used for the stratification were from the Interactive Voice Response System (IVRS)-indicated data rather than the actual data recorded in the case report form (CRF). This error has been corrected in a CSR Erratum included in this submission (Mod5.3.5.1/EPOANE3021 CSR Erratum). A brief description is also provided in the Section DATA NOTIFICATION AND CORRECTION at the end of this response document.

Assessor's comment

Further analyses in order to better characterize the impact of transfusion on erythroid response rate were requested below (comments).

Issue partially solved

QUESTION-9

There were 2 events contributing to the overall composite primary endpoint:

a) **≥1.5 g/L Hb increase from baseline**

b) **Reduction of RBC transfusions of at least 4 units for 8 weeks compared to transfusion performed within the 8 weeks before treatment.**

Results for the 2 individual events should be provided by the MAH.
Moreover the MAH should confirm that only RBC transfusion given for a Hb ≤ 9.0 g/dL pre-treatment was counted in the RBC transfusion response evaluation as stated in the 2006-IWG response criteria. Otherwise, a sensitivity analysis of the primary endpoint should be performed, taking into account this condition.

APPLICANT RESPONSE

The RRC review was conducted based on formatted extracts from the database showing all relevant elements to assess response according to the IWG 2006 criteria. The programming included the condition that only transfusions given for pre-transfusion Hb levels of ≤9 g/dL within 8 weeks prior to baseline would be counted as pre-treatment transfusion needs for each subject. This approach has preemptively taken the IWG2006 condition into account, and therefore, no sensitivity analysis was performed.

In the EPOANE3021 study, 2 of 29 (6.9%) responders were assessed based on their red blood cell (RBC) transfusion decrease by the RRC, and the remaining 27 of 29 (93.1%) responders were assessed based on their Hb changes according to the IWG2006 criteria (Table 10). The 2 responders (and) assessed based on their RBC transfusion decrease (both in the epoetin alfa group) required a transfusion of 4 units of blood within 8 weeks prior to randomization, and became transfusion independent (receiving no blood transfusion for at least 8 weeks) in the first 24 weeks.The thoroughness of RRC review for the transfusion according to the IWG2006 criteria is described in more detail in the Applicant's response to Question-12. For example, 1 subject ( ) was considered by the investigator as a responder due to a decrease in transfusion need. However, the RRC noted that the transfusion rule applied to this subject was inconsistent during the study (eg, for the same condition of Hb ≤9 g/dL, the subject received a transfusion prior to randomization, but did not receive a transfusion after enrollment in the study). Therefore, the RRC disqualified this subject as a responder due to the inconsistency in applying the transfusion rule (Table 10).

Assessor's comment Results were provided by the MAH as requested by the CMDH and indicate that most of positive response to treatment were based upon the Hb increase ≥ 1.5 g/L (93%).

However, further analyses in order to better characterize the impact of transfusion on erythroid response rate were requested below (comments).

Issue partially solved

QUESTION-10

Finally, the impact of the RBC transfusions on the Hb change is not clear, a new sensibility analysis is required, the Hb values of >1.5 g/L from baseline after three week of the last RBC transfusion should not be consider as positive erythroid response, the MAH should assess the data again considering only positive Hb response after three week transfusion

free, the clinical relevance of the results obtained from this re-analysis in comparison with the main results of the primary endpoint should be discussed. (comments)

APPLICANT RESPONSE

The Applicant agrees that the impact of RBC transfusion on the change in Hb levels needs to be carefully considered when evaluating the erythroid response according to the IWG2006 criteria in the EPOANE3021 study. Exactly for this reason, the RRC was commissioned during the study by the Applicant to provide clinical review expertise for determination of erythroid response using the IWG 2006 criteria. Particularly, the Applicant emphasized in the CSR that it is possible that the effect of blood transfusions on Hb levels could result in inappropriately positive assessments of response, if not assessed carefully for each subject. Since the application of the IWG 2006 response criteria by investigators during the study may have varied given the above issues, the RRC was appointed to ensure a consistent approach to the response assessment. Moreover, in the RRC Charter (see initial application: CSR EPOANE3021/App 9 [Mod5.3.5.1]), it was clearly stated "NOTE: All assessments of Hb should be based on untransfused Hb, i.e., the subject did not receive an RBC transfusion within the previous week."

It has been noted that the extent of Hb change in response to RBC transfusion varied in subjects in the EPOANE3021 study, depending on several conditions, including the state of individual patient and their disease circumstances, as well as the blood product conditions etc. The Applicant believes that the RRC assessment for the primary and major secondary efficacy endpoint, erythroid response according to the IWG2006 criteria, in the EPOANE3021 study was thorough and in-depth. The expert members of the RRC carefully reviewed each subject's record and situation, prudently assessed each subject's transfusion state, before making their final adjudication report. Especially, the dynamics of the individual Hb levels after transfusion were taken into account by the RRC when assessing the erythroid response.

This is evidenced in the list of discrepancies in evaluation of erythroid response at Week 24 according to IWG2006 criteria between the RRC assessment and the investigators' reports (CRF) in the EPOANE3021 study (see Applicant's response to Question-12). The expert members of the RRC thoroughly and carefully considered the potential impact of the blood transfusion on the increase of Hb level in each subject. As result, a total of 8 subjects who were responders according to the CRF were assessed by the RRC as non-responders, because the RRC considered the increase in these subjects' Hb levels were affected by the transfusions they received prior to Week 24. In addition, the RRC had also carefully assessed the stability and duration of each of the subjects' responses. As a result, 4 subjects whom the investigators evaluated as responders were disqualified by the

RRC assessment: 2 of the subjects due to their response stabilities, and 2 of the subjects due to their response durations (see Applicant's response to Question-12).

In summary, a key responsibility of the RRC for the EPOANE3021 study was to carefully assess and rule out an impact of the RBC transfusions on Hb changes for the primary and major secondary efficacy endpoint of the study. The Applicant believes that the members of the RRC had diligently conducted their assessment and the primary and major secondary efficacy outcome results of the EPOANE3021 study are valid and reliable.

Assessor's comment

It is unclear if RRC assessments of Hb were based on untransfused patients within the previous week of Hb assessment or any transfusion prior to week 24. The requested additional analysis excluding untransfused responder patients within 3 weeks prior Hb assessment free would have been useful to comfort the Applicant's conclusion.

The primary efficacy parameter is defined by the demonstration of ER according to IWG 2006 criteria at any time during the first 24 weeks of the study. In the document of statistical methods and interim analysis plans (section 5.2), it was mentioned that the RRC will reassess the ER endpoint to ensure consistency of its assessment. The following data were assessed by the RRC: 1. Assessment for each subject if ER was demonstrated up to Week 24 for a period of at least 8 weeks (Yes/No); 2. The week (number) the subject starts to show ER; 3. The last week (number) the subject shows ER; 4. Assessment for each subject if ER was demonstrated at Week 24 (Yes/No); 5. Any additional comments regarding ER for a subject that the RRC members find relevant. These criteria allowed an individualized assessment of each subject taking into account the stability of the response.

Globally, higher statistically significant difference in time to first RBC transfusion after Week 4 in the epoetin alfa group compared with the placebo group and a decrease in the percentage of subjects with transfusions over time through Week 24 was observed in the epoetin alfa group; whereas, an increase was observed in the placebo group.

Finally, even if the percentage of erythroid response has not been consolidated, the approach chosen by the MAH seems reasonable.

Issue solved

QUESTION-11

The OS results of the Italian registry only show an OS benefit for EPO treatment in patients with baseline Hb levels between 8 and 10 g/dL who are not transfusion dependent.

Thus, the MAH should discuss the benefit of Eprex treatment for patients who have Hb levels less than 8 g/dL at baseline or are already transfusion dependent (comments).

APPLICANT RESPONSE

The information related to subjects in the EPOANE3021 study with a baseline Hb <8 g/dL, including their actual baseline Hb levels, transfusion needs (8 weeks prior to the baseline), the erythroid responses according to the IWG2006 criteria, and the decrease in transfusion is summarized in the Table 9 below.

Table 9: Subjects in the EPOANE3021 Study with Baseline Hemoglobin < 8 g/dL

Subject Number	Baseline Hemoglobin (g/dL)	Transfusion Units (8 weeks prior to baseline)	sEPO at screening (mU/mL)	Erythroid Response (IWG2006)	Decrease in Transfusion need*
Epoetin Alfa (11)					
	7.2	4	54.6	no	no
	7.8	2	695	no	no
	7.1	4	87	no	no
	7.81	2	60	yes	yes
	7.6	2	352	no	yes
	7.9	0	20.8	yes	NA
	7.85	3	63.8	no	no
	6.76	2	499.5	no	no
	7.32	3	337	no	no
	7.57 (4.7 mmol/L)	4	102	no	no
	7.3	2	492	no	yes
Placebo (5)					
	7.5	2	51.3	no	no
	7.6	2	74.5	no	no
	7.62	3	287	no	no
	7.5	3	165	no	no
	6.9	3	124	no	no

*: decrease in transfusion needs, but not enough to meet the IWG2006 requirements.
Source: EPOANE3021 Study Database Excel Files: EPOANE3021_Treatment unblinding codes;

EPOANE3021_Screening and Baseline hemoglobin values randomized subjects, EPOANE3021_Transfusions blinded phase; EPOANE3021_RRC report core phase; EPOANE3021_RRC response review spreadsheet and transfusions summary.

As indicated in Table 9, there were 16 subjects with baseline Hb <8 g/dL, 11 of 85 (13%) subjects in the epoetin alfa group and 5 of 45 (11%) subjects in the placebo group. All needed 2 to 4 units of transfusions within 8 weeks prior to baseline with exception of 1 subject in the epoetin-alfa group who did not require any transfusions.

Among subjects with Hb <8 g/dL in the epoetin alfa group, 2 of 11 (18.2%) subjects (and) were responders in the first 24 weeks based on the IWG2006 criteria assessed by the RRC, which was lower in comparison with the response rate in subjects with baseline Hb ≥8 g/dL ([27-2]/[85-11], 25 of 74 [33.8%]). Both of these 2 subjects had low or no transfusion requirements at baseline and a low sEPO level. Two of 11 (18%) subjects (,) in the epoetin alfa group had reduced transfusion needs, but did not meet the IWG2006 requirements. Both had low transfusion requirements at baseline (2 units/8weeks) and a sEPO level >200 mU/mL.

All 5 subjects with Hb <8 g/dL in the placebo group were non-responders in the first 24 weeks based on the IWG2006 criteria assessed by the RRC, and none of them had decrease in transfusion needs.

Due to the small number of subjects with Hb <8 g/dL, it is difficult to draw any conclusion regarding a correlation between erythroid response and baseline Hb level. However, the results in this subpopulation showed a benefit to treat subjects with baseline Hb <8 g/dL, as long as their baseline sEPO level is low and their baseline transfusion requirement is limited.

In the Italian MDS registry report (see initial application: Italian MDS Registry Study [Mod5.3.5.4]), the investigators compared the erythroid response rate to erythropoietin (EPO) between 2 groups of patients: “transfusion dependent with baseline Hb <8 g/dL” and “non-transfusion dependent with baseline Hb 8-10 g/dL”. The investigators reported that “the response rate to EPO was significantly higher in non-transfused patients than in transfused patients: 69% versus 14% respectively (p value < 0.001).” In addition, analysis of overall survival (OS) within each group showed that EPO treatment clearly improved the OS of the patients with Hb 8-10 g/dL (median survival: EPO vs. non-EPO, 64 months vs. 43 months respectively, p<0.001). The difference in survival by EPO therapy was not

evident in transfusion dependent patients with Hb <8 g/dL when compared with patients who did not receive EPO (p=0.6).

The results of EPOANE3021 study discussed above showed that not every subject with baseline Hb <8 g/dL was transfusion-dependent. It is not clear from the Italian MDS registry study report how the transfusion dependency was defined in those patients with baseline Hb <8 g/dL.

In the literature, multivariate analyses of predictors of response in MDS were reported in a number of studies. Baseline sEPO level was considered the most frequently reported significant predictor (see initial application: Literature review/Sec 4.3.1.1.3 [Mod5.3.5.4]). In a study with a similar patient population as the EPOANE3021 study (Latagliata 2008)[11], 11 of the 32 transfusion-dependent patients (34.3%) achieved a reduction in transfusion requirement after a median time of 9 weeks and 8 of 11 patients became transfusion-free. The baseline Hb levels in responders were 8.8 ± 1.2 g/dL, indicating that some of the patients had Hb levels <8 g/dL at baseline. In the study by Rose at al. (1995)[18], 10% of patients achieved an increase in hematocrit and 19% of patients had transfusion reduction. MDS patients in this study had a baseline Hb <8 g/dL and 90% of them required transfusions. Characteristics for responders and non-responders were similar with respect to age, sex, transfusion requirements and baseline hematocrit. Patients with sEPO <100 mU/mL were most likely to respond.

In a study by Hellstrom-Lindberg (1995)[9], a difference in response between requiring and not requiring transfusion was observed (10% vs 44%, p<0,001). Latagliata et al (2008)[11] reported that transfusion-dependent patients had worse response than that of transfusion-free patients. The result is in the same direction (but larger) as reported in Hellstrom-Lindberg[9]. The Italian Cooperative Study Group (1998)[10] also reported that the response rate in non-transfused patients was approximately 3 times higher than that in transfused patients. However, transfusion dependency had no predictive value for response to treatment in the Terpos study that investigated whether prolonged administration of erythropoietin increases erythroid response rates (Terpos-2002)[20]. Results showed that prolonged administration of rHuEpo (subcutaneously, at a dose of 150 U/kg three times weekly, for a minimum of 26 weeks) can increase response rates independent of transfusion dependency. A response rate of 45.1% was obtained after 26 weeks of treatment. Responders and non-responders did not differ with respect to transfusion dependency.

According to the studies by Latagliata (2008)[11] and Italian Cooperative Study Group (1998) [10], the baseline Hb level was a predictor for erythroid response. Latagliata et al[11] demonstrated that for each 1 g/dL increase in the baseline Hb level, the probability of response increased by 98%.

MDS patients with Hb levels <8 g/dL are often in need of transfusion. Transfusion need is a sign of severe MDS and has been shown to correlate with both the degree of erythroid dysplasia and with the presence of trilinear dysplastic changes in the bone marrow. It is likely that the maturation is more defective in these patients and that less epo-responsive cells are present in the bone marrow (Hellstrom-Lindberg 1992)[8]. Although the information is limited about the benefit of ESA treatment in MDS patients who have Hb levels <8 g/dL at baseline or are already transfusion dependent, the available data indicate that there is a benefit for this subpopulation.

Depending on the refractory anemia subtype of MDS, combination therapy or longer treatment may increase response rates. Reports on patients with ring sideroblasts receiving treatment with EPO in combination with other cytokines such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have suggested that such combinations may be more effective with response rates as high as 50% and 60% in this patient population (Negrin et al, 1993; Hellstrom-Lindberg et al, 1993; Hansen et al, 1993) [15,7,6]. In addition, regimens as used in the current study should be compared to combination treatment and prolonged treatment duration, especially when considering the costs.

In summary, several factors are associated with response to ESA therapy, including the subtype of MDS, sEPO levels, no or limited transfusions prior to treatment and baseline Hb levels. Among them, the baseline sEPO level has the strongest predictive value. Based on the limited data available, whether a patient with a baseline Hb level <8 g/dL should be treated with and could benefit from epoetin alfa therapy will be largely dependent on the patient's conditions, such as sEPO level, transfusion status and comorbidities, as well as the therapy strategies, such as the use of a combination therapy and the treatment duration.

Assessor's comment

Due to the small size in patients who have Hb levels less than 8 g/dL at baseline and are already transfusion dependent in EPOANE 3021 study, we agree with the MAH that it is not possible to conclude the benefit of the drug in this subgroup of patients. Basing on these data, the dependence transfusion should not be considered as a restriction in EPREX indication.

Issue solved

QUESTION-12

The higher rate of erythroid response in epoetin alfa group than in placebo group was confirmed at Week 24 with both the RRC and investigator evaluation and in both ITTm and PP analysis evaluation. Nevertheless, there are discrepancies between investigators and

RRC response evaluations. Disagreements should be detailed and discussed (number of responders versus non responders disagreements and if any, number of disagreements in positive response to treatment: ≥ 1.5 g/L versus < 4 units RBC transfusion).

APPLICANT RESPONSE

A detailed list of discrepancies in the evaluation of erythroid response at Week 24 according to IWG2006 criteria between the RRC assessment and the investigators' reports (CRF) in the EPOANE3021 study is provided in Table 10 below.

In the EPOANE3021 study, the expert members of the RRC thoroughly and carefully considered the potential impact of the blood transfusion on the increase of Hb level in each of the enrolled subjects, as evidenced in the information provided in Table 10. A total of 8 subjects who were responders according to the CRF were assessed by the RRC as non-responders, because the RRC considered the increase in these subjects' Hb levels to have been affected by transfusions they received prior to Week 24.

The RRC had also carefully assessed the stability and duration of each of the subjects' responses. As result, 4 subjects who were responders according to the CRF were disqualified as responders by the RRC: 2 of the subjects due to their response stabilities, and 2 of the subjects due to their response durations. There were also some subjects who were considered as non-responders according to CRF based on their baseline Hb levels, but were assessed as responders by the RRC. For example, one subject ( ) who was considered as a non-responder according to the CRF due to a single point Hb fluctuation at the Week 24 was assessed by the RRC as a responder, since the subject's response was otherwise and overall stable (see Table 10).

Table 10: Discrepancies in Evaluation of Erythroid Response at Week 24 According to IWG2006 Criteria Between the RRC Assessment and the Investigators' Reports (CRF) in the EPOANE3021 Study

Responders at Week 24 per RRC	Responders at Week 24 per CRF	Comment
		Hb increase due to transfusion prior to Week 24
		Hb increase due to transfusion prior to Week 24
		Hb increase due to transfusion prior to Week 24
		Based on baseline Hb, the subject was assessed as non-responder by the site. However, the RRC noted that the baseline Hb was largely influenced by a transfusion conducted between screening and baseline visit, and therefore, decided to use screening Hb as baseline for response assessment. Based on the screening Hb value, the subject was assessed as a responder.

		There was a Hb fluctuation at Week 24, so the site assessment was "No" for this visit. Otherwise the subject was demonstrating a stable response on the lowest dose of epoetin alfa with several dose holds for Hb >12 g/dL, Based on the overall information from the subject, the RRC assessed the subject as a responder.
		Hb increase due to transfusion prior to Week 24
		The RRC considered the subject's response between Weeks 17 and 33 as unstable and therefore assessed the subject as a nonresponder at Week 24
		The subject was withdrawn from the study at Week 20, demonstrating stable response even the treatment was stopped from Week 5. There were no data in the CRF for Week 24, thus, the subject was listed as a non-responder by the site. However, the RRC noted that the subject's response was still present at the early withdraw visit which occurred on Week 24, and, therefore, assessed the subject as a responder at Week 24.
		The site considered the subject as responder due to decrease in transfusions. However, the RRC noted that the transfusion rule applied to this subject was inconsistent during the study (eg, for the same condition of Hb <9 g/dL, the subject received transfusion prior to randomization, but did not receive transfusion after enrolled in the study). Therefore, the RRC disqualified the subject as a responder due to the inconsistency in applying the transfusion rule.
		There was a Hb decrease at Week 24 because of a preceding dose hold due to Hb >12 g/dL. However, there was a response continuing at Week 25. Based on the overall information from the subject, the RRC assessed the subject as a responder.
		Hb increase due to transfusion prior to Week 24
		Hb increase due to transfusion prior to Week 24
		The RRC considered the subject's response not stable enough to be qualified as a responder per IWG2006 criteria, although the RRC noted that subject had benefit from the therapy.
		The 8-week duration requirement for IWG2006 response criteria was not met on the maximum dose.

		The 8-week duration requirement for IWG2006 response criteria was not met on the maximum dose. The RRC commented that the information from this subject was difficult to interpret as there were a number of AEs which could have masked a response in this subject.
		Hb increase due to transfusion prior to Week 24
		There was a single point Hb at Week 24 below the response margin (1.4 g/dL) and response margins were reached both at Weeks 23 and 25 (see Data Notification and Correction Section of this response document and the CSR Erratum). The RRC performed a reassessment and decided to keep the subject's response status, but change the response duration from 23 weeks to 25 weeks.

		The subject was noted by the RRC as having clinical benefit from the therapy but not sufficient to meet the IWG2006 response criteria due to the baseline Hb value. The RRC noted that if an average of the screening and baseline Hb level was taken as the baseline Hb value (as per IWG2006 guidelines, not per the practice in the study) the subject would be considered as a responder.
		Hb increase due to transfusion prior to Week 24
		no disagreement
		no disagreement / response due to transfusion independence
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement
		no disagreement / response due to transfusion independence
		no disagreement
		no disagreement
		no disagreement

AEs = adverse events; CRF = case report form; Hb = hemoglobin; IWG = International Working Group; RRC = Response Review Committee;
Source: EPOANE3021 Study Database Excel Files: EPOANE3021_ER at W24 as recorded in the CRF; EPOANE3021_RRC response review spreadsheet and transfusions summary; EPOANE3021_RRC report core phase.

Assessor's comment

As requested by the CHMP, the MAH provided the detailed of discrepancies between investigators and RRC response evaluations. In Table 10 have been listed all the responders at Week 24 (in both placebo and EPO arms). There was no disagreement for 19 responders between investigators and RRC assessments. 8 subjects were responders according to the CRF and were assessed by the RRC as non-responders, because the RRC considered the increase in these subjects' Hb levels to have been affected by

transfusions they received prior to Week 24. RRC and investigators were in disagreement in 11 subjects. The causes of these disagreements have been well detailed.

Despite these disagreement, the higher rate of erythroid response in epoetin alfa than in placebo group was confirmed at Week 24 with both the RRC and investigator evaluation.

Issue solved

QUESTION-13

Based on the RRC assessment of responders set at any time during the first 24 weeks in the mITT analysis, subjects in the epoetin alfa group had a higher mean response duration of day than in the placebo group through completion of this 52-week study (192.3 ± 88.92 vs 99.0 ± 69.30 days). Comparing to a published study (Park et al., 2008[a]) evaluating data from French and Belgian hematologic centers of the Groupe Francophone des Myelodysplasies (GFM) with 403 patients, median duration of response from the onset of rHuEPO was 24 months according to IWG 2006 criteria which is much higher than in this study. The MAH should discuss these observed discrepancies.

APPLICANT RESPONSE

In the EPOANE3021 study, based on the RRC assessment of subjects in the mITT analysis set who had an erythroid response at any time during the first 24 weeks, the median duration of erythroid response through completion of this 52-week study was 197 days (based on 27 subjects) in the epoetin alfa group and 99.0 days (based on only 2 subjects) in the placebo group. In a report published by Park et al, in 2008[16], the median response duration was reported as 24 months according to IWG 2006 criteria.

There were several study design differences between the EPOANE3021 study and the study described by Park et al, in 2008:

- Study type

  The EPOANE3021 study was a randomized, double-blind, placebo-controlled confirmatory clinical study, whereas the study that Park et al reported in 2008 was a registry type of study, which was observational, similar to the 3 registry studies included in the application (see initial application: Mod5.3.5.4) submitted on 24 March 2016. Moreover, comparable median response durations were observed among these registry studies: 24 months (Park 2008)[16], 25 months (French MDS Registry), 82 weeks (~18.9 months) (Italian MDS Registry), and 21.7 months (Spanish MDS Registry).

[16] Park S et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008 Jan 15;111(2):574-82.

- Control group

  In the EPOANE3021 study, a placebo control group (with standard care) was used as a comparison, whereas in the study that Park et al reported in 2008[16], a historical cohort, where MDS patients had received only supportive care from the International MDS Risk AnalysisWorkshop (IMRAW) database was used for comparison.

- Study agent

In the EPOANE3021 study, only epoetin alfa (EPREX) was investigated, whereas in the study that Park et al reported in 2008, results were from patients treated with various ESAs, including epoetin alfa, epoetin beta, and darbepoetin alfa. In addition, some patients also received G-CSF or lenograstim treatment. The response duration assessment was based on the entire study population including those with various ESAs and G-CSF.

- Posology:

  In the EPOANE3021 study, dosing of epoetin alfa was weight-based (IU/kg) with a lower starting dose, weekly Hb monitoring and stringent rules for dose hold or decrease, whereas in the study that Park et al reported in 2008, an absolute dose of 60,000 IU per week epoetin alfa was used, and no stringent dosing rules were mentioned.

In summary, the Applicant believes that these above mentioned differences make it difficult to directly compare the response duration between these 2 studies.

Assessor's comment

As requested by the CHMP, the MAH detailed all design differences between the EPOANE3021 study and the study described by Park et al, in 2008 explaining the higher median duration of response in Park study which are acceptable.

Issue solved

SAFETY

QUESTION-14

In order to clarify the adverse events related to study agent, the MAH should provide a table of all adverse events of the first 24 weeks and of the entire period, precising if the adverse effect is related or not to study agent. Adverse events doubtfully, possibly, probably, very likely related to study agent should be considered as related to study agent.

In addition, frequencies of AEs during the first 24 weeks vs. extension phase should be compared (comment).

APPLICANT RESPONSE

Adverse Events in Relationship to Study Agent

Treatment-emergent adverse events in relationship to study agent were analyzed and results are provided in attachments, including those for the first 24 weeks (Attachment TSFAE13a), for the extension period (Attachment TSFAE13b), and for the entire study (Attachment TSFAE13c).

The most frequently reported AE during the first 24 weeks that was considered as at least doubtfully related to study agent was constipation (in 2.4% of subjects of the epoetin alfa group). The majority of the AEs with relationship to study agent were doubtfully or possibly related. Two cases in the epoetin alfa group were considered as "very likely" related to study agent. One case ( ) was related to an event of "distal deep venous thrombosis in the lower leg", which is discussed in more details in the response to Question-15. The other case was cited as "injection site discomfort". During the extension phase of the study, the only case in the epoetin alfa group that was considered as "very likely" related to study agent was "anti-erythropoetin antibody positive". This case ( ) has been described in detail in the CSR, and there were no signs of pure red cell aplasia in the bone marrow for this subject (see initial application: CSR EPOANE3021/Sec 7.2.2.2.3 [Mod5.3.5.1]).

Comparison of the Frequency of Adverse Events During the First 24 Weeks vs. the Extension Phase

The frequency of AEs during the first 24 weeks was provided in the CSR (see initial application: CSR EPOANE3021/Att TSFAE01c [Mod5.3.5.1]), and re-supplied in this response document for convenience of the review: Attachment TSFAE01c. The frequency of AEs during the extension phase of the study is provided in Attachment TSFAE01f.

Since only 1 subject in the placebo group entered the extension phase, the comparison of the incidences of AEs therefore is focused only on subjects in the epoetin alfa group between these 2 study periods.

In addition, the term "after 24 weeks" has a different meaning from the term "in the extension phase": the former included all subjects after the 24 week treatment period regardless of whether they entered the extension phase; whereas the later included only those who entered the extension phase. Thus, AEs occurred after the first 24-week

treatment phase in subjects who did not enter the extension phase would not be included in the discussion below.

Some selected key safety findings for the first 24 weeks and for the extension phase of the study are displayed in Table 11.

Table 11: Summary of Selected Key Safety Findings for the First 24 Weeks and for the Extension Phase in the EPOANE3021 Study (Study EPOANE3021: Safety Analysis Set)

	First 24 Weeks	Extension Phase[a]
	Epoetin Alfa	Epoetin Alfa
Analysis set: safety	85	39
Subjects reporting:		
At least 1 treatment-emergent adverse event	66 (77.6%)	27 (69.2%)
Discontinuation of study	15 (17.6%)	10 (25.6%)
Deaths	4 (4.7%)	1 (2.6%)
At least 1 thrombotic vascular event	4 (4.7%)	0
Disease progression (including progression to acute myeloid leukemia)	11 (12.9%)	3 (3.5%)
Progression to acute myeloid leukemia	3 (3.5%)	0

[a] At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase. Therefore, only data from the epoetin alfa group are compared.

Source: initial application: CSR EPOANE3021/Fig 3 and Att TSFAE01c (Mod5.3.5.1); Attachment TSFAE01f.

Results are summarized below:

- Treatment –emergent adverse events occurred in 66 of 85 (77.6%) subjects during the first 24 weeks and 27 of 39 (69.2%) subjects in the extension phase. This difference may be partially attributed to a higher study discontinuation rate during

  the extension phase, where discontinuation due to lack of efficacy could take place (15 of 85 [17.6%] subjects during the first 24 weeks and 10 of 39 [25.6%] during the extension phase) (see initial application: CSR EPOANE3021/Fig 3 [Mod5.3.5.1]).
- The type of the most frequently (>6% in either study period) occurred AEs was similar between these 2 study periods, and the incidence rates of these AEs for the first 24 weeks vs. the extension phase were: asthenia (14.1% vs. 5.1%), fatigue (9.4% vs. 5.1%), diarrhea (9.4% vs. 5.1%), dyspnea (9.4% vs. 7.7%), pyrexia (8.2% vs. 7.7%), nausea (4.7% vs. 7.7%), nasopharyngitis (7.1% vs. 10.3%), and constipation (7.1% vs. 5.1%). (see initial application: CSR EPOANE3021/Att TSFAE01c [Mod5.3.5.1]) and Attachment TSFAE01f.
- The rate of disease progression was higher during the first 24 weeks in comparison to the extension period (12.9% vs. 3.5%) (see initial application: CSR EPOANE3021/Att TSFREL01 and TSFREL03 [Mod5.3.5.1]). Among them 3.5% subjects with disease progression to AML during the first 24 weeks and none of the subjects progressed to AML during the extension period. All cases of TVE occurred

during the first 24 weeks, and no TVEs were reported during the extension phase. More detailed information related to these TVE cases is provided in response to Question-15. Death occurred in 4 subjects (4.7%) during the first 24 weeks, and in 1 subject (2.6%) during the extension phase (sudden death). More detailed information related to all death cases is provided in response to Question-16.

Assessor's comment

In order to clarify the adverse events related to study agent, the MAH provided a table of all adverse events of the first 24 weeks and of the entire period, precising if the adverse effect is related or not to study agent.

During the first 24 weeks, the majority of the AEs with relationship to study agent were doubtfully or possibly related. Two cases in the epoetin alfa group were considered as "very likely" related to study agent: one case ( ) was related to an event of "distal deep venous thrombosis in the lower leg" and one case of "injection site discomfort". During the extension phase of the study, the only case in the epoetin alfa group that was considered as "very likely" related to study agent was "anti-erythropoetin antibody positive". The type of the most frequently (>6% in either study period) occurred AEs was similar between these 2 study periods. No new safety signal emerged from this study.

Issue solved

QUESTION-15

The MAH should document for all patients presented a TVE the Hb level at the baseline, the delay and the intensity of the response to the drug, the Hb level at the response, the additional risk factor, the concomitant treatment. These informations could lead to any recommendations for the use of EPO alfa in elderly patients with additional risk (e.g. PIL).

APPLICANT RESPONSE

In the EPOANE3021 study, as described in response to Question-4 of this document, there was an imbalance in medical history, which showed a higher percentage of subjects with history of cardiovascular events in the epoetin alfa group than that in the placebo group: eg, atrial fibrillation (8.2% vs. 2.2%), coronary artery disease (7.1% vs. 4.4%), myocardial ischemia (4.7% vs. 0), diabetes (placebo: 6.7%, EPO: 17.6%), although the incidence of hypertension was higher in the placebo group than that in the epoetin alfa group: (62.2% vs. 49.4%) (see initial application: CSR EPOANE3021/Att TSIMH01 [Mod5.3.5.1]). In addition, a subject with any suspected TVE, no matter if it was confirmed or not, was counted as having a TVE in this study. Under these circumstances, a total of 4 subjects (all in the epoetin alfa group) were reported to have TVEs.

Information related to these subjects' baseline Hb level, their responses to the study agent, as well as the Hb level at the time of response, etc. was provided in the brief narratives in Section 7.2.2.4.1.1 of the CSR, as well as in the full narratives in the Attachment of the CSR (see initial application: CSR EPOANE3021/ Sec 7.2.2.4.1.1 and Att Narratives [Mod5.3.5.1]).

For the convenience of review as requested by the Agency, the information related to the TVE events of these subjects is also summarized in Table 12 below.

Table 12: **Subjects with Thrombotic Vascular Events in the EPOANE3021 Study (all with Onset in the First 24 Weeks and in the Epoetin Alfa Group)**

Subject ID Age/Sex	Verbatim/ Preferred Term/	Hb level at baseline	Hb level around the TVE	Erythroid response status around TVE	Relevant medical history	Relevant concomitant medications	Additional relevant information
73/Male	Ischemic Stroke/ Ischaemic Stroke	7.1 g/dL	9.7 g/dL	No response	chronic atrial fibrillation, heart failure,	dabigatran,	a CT scan on Day 105 during a hospitalization for investigation of cachexia revealed an old ischemic infarct in the subcortical white matter. died of cachexia on Day 203;
75/Female	Phlebitis/ Phlebitis	11.0 g/dL	10.8 g/dL (9 days after the TVE)	No response	left calf pain and superficial thrombophlebitis hypercholesterolemia	pravastatine	The subject received only one injection of the study agent before the event. Study agent was discontinued due to this event.
71/Female	Sudden Death/ Sudden Death	7.8 g/dL	9.1 g/dL (2 days prior to death).	No response	None	prednisone,	Subject died at home, and was not seen by a physician prior to the death. Primary physician suggested that the possible reason of death was stroke.
77/Female	Thromboembolic Event/ Embolism	9.7 g/dL	12.8 g/dL	Yes (Week 12 to Week 20, duration: 54 days)	None	None	Due to the TVE event, treatment with epoetin alfa was interrupted from Day 127 to Day169. Following the resolution of the TVE, the subject continued epoetin alfa therapy in the extension (W48) and was subsequently enrolled in the Open label phase for 6 more months.

Note: Adverse events terms are coded using MedDRA/E version 14.0.
CT = computed tomography; Hb= hemoglobin; TVE = thrombotic vascular events
Source: initial application: CSR EPOANE3021/ Sec 7.2.2.4.1.1, Attachment of Subject Narratives, LSIMH01, LSFAE01a, LSFLAB01a (Mod5.3.5.1)

As indicated in Table 12 above, among the 4 subjects reported to have TVEs, the first 2 subjects had medical history related to thrombotic events: the subject ( ) had a history of atrial fibrillation and heart failure, a CT scan revealed an old ischemic stroke with the event onset date unknown, and the subject ( ) had a medical history of superficial thrombophlebitis who reported an event of phlebitis during the study. Since the subject had Doppler confirmed distal deep venous thrombosis, this case was included as a TVE case. The third subject (, 71 years old) died suddenly. A stroke was suspected afterwards by the physician as the cause of sudden death, which was never confirmed, and no autopsy was performed. For conservative purpose, this case, although no thromboembolic event reported, was included as a TVE case. The subject had no medical history of thrombotic events. As indicated in both the CSR and the clinical summary documents, all the above 3 subjects were non-responders according to the IWG2006 criteria assessed by RRC.

The last subject ( ) had no medical history of thrombotic events and responded to the epoetin alfa treatment according to the IWG2006 criteria assessed by RRC. She developed embolism (distal deep venous thrombosis in the lower leg, diagnosed with Doppler) in Week 18, during her response period. Thus, although 4 subjects in the EPOANE3021 study were reported with TVEs, only 1 subject who lacked significant risk factors actually had a confirmed treatment-emergent TVE during the treatment period. After the TVE was resolved, the subject continued on a lower dose and completed the extension phase of the study without occurrence of further TVEs. Although Hb has increased prior to onset of TVE, it is very difficult to draw any conclusion or provide recommendation based on this single case.

Thrombotic vascular event is a known risk factor associated with the use of the ESAs. However, since 2 of the 3 confirmed TVE cases in the study had a medical history related to thrombotic events, an appropriate prophylaxis and careful risk-benefit assessment will be necessary before initiating or continuing epoetin alfa therapy in such patients.

Assessor's comment

The Rapporteur does agree that it is difficult to propose recommendations based on the few cases presented which moreover all have a particular history which makes the homogenization of such a small series difficult. The Rapporteur considers that the mention of the risk of TVEs in the SmPC section 4.4 is sufficient: "*The reported risk of these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with*

pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident). In all patients, haemoglobin levels should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the concentration range for the indication of use".

Issue solved

QUESTION-16

Eight deaths were observed during the entire study period due to treatment-emergent adverse events (7 in the epoetin alfa group and 1 in the placebo group). None of the deaths were considered related to study agent by the investigators. However, in 5 deaths, investigations revealed that all these cases concerning elderly patients with history of renal insufficiency, of hypertension or cardiovascular pathology. The MAH should further discuss these cases taking into account these comorbidities. As required above, the MAH should propose some recommendations of the use of EPO alfa in elderly patients with comorbidities.

APPLICANT RESPONSE

For all subjects who died during the EPOANE3021 study, detailed information related to their ages and comorbidities was provided in each of the brief narratives in the Section 7.2.2.1.2, and also in the full narratives as the Attachment of the CSR (see initial application: CSR EPOANE3021/ Sec 7.2.2.1.2 and Att Narratives [Mod5.3.5.1]).

For the convenience of review, the comorbidity information in subjects who died in the EPOANE3021 study is summarized in Table 13 below.

Among the 8 subjects who died in the EPOANE3021 study, 4 subjects (, , ,) had cardiac/renal related comorbidities, 3 subjects (, ,) had MDS disease progression and 1 subject ( ) had a sudden death with unclear cause. As indicated in the Section 9 of the CSR, due to the low number of deaths, the elderly and co-morbid population studied, and no common reason for the deaths, no conclusion for a link between epoetin alfa therapy and a fatal outcome can be drawn.

Several reports in the literature have indicated that at least 50% of MDS patients have some comorbid condition (Della Porta 2009, Naqvi K 2011, Sperr WR 2010, Wang R 2009) [1,13,19,22]. In the Spanish MDS Registry report, 45% (218 out of 483 patients) in the ESA arm showed comorbidities (see initial application: Spanish registry study [Mod5.3.5.4]). The presence of comorbidities has also been shown to affect the survival

rate (Naqvi K 2011)[13]. The association between comorbidities and survival, independent of IPSS risk, has been shown in numerous studies that have measured comorbidity using various tools, such as the Hematopoietic Stem Cell Transplantation-Specific Comorbidity Index (HCT-CI) (Zipperer 2009)[24], the Adult Comorbidity Evaluation-27 instrument (ACE-27) (Naqvi K 2011)[13] and the MDS-Specific Comorbidity Index (MDS-CI) developed by Italian investigators (Della Porta 2011)[1].

Five comorbidity conditions that impact survival in MDS patients were identified by Della Porta et al (2011)[1]: cardiac disease, solid tumor, moderate to severe hepatic disease, severe pulmonary disease and renal disease. These 5 comorbidities were found to be independently associated with the risk of non-leukemic death in multivariable analysis. When integrating them with the WHO Classification-Based Prognostic Scoring System (WPSS), the MDS-CI showed a significant effect on overall survival in the very low/low and intermediate WPSS risk subgroups (P <0.001). The analysis confirmed the prognostic value of comorbidity in MDS.

However, none of these tools alone explicitly focuses on the elderly MDS patient. The National Comprehensive Cancer Network (NCCN) MDS Panel, therefore, makes no specific recommendation for which comorbidity index to use, but does recommend thorough evaluation of the presence and extent of comorbid conditions in the management of MDS (NCCN Guidelines 2016)[14]. MDS occurs primarily in elderly patients who often have comorbidities. There is no one easy way to keep older patients with MDS on their treatments, yet doing so is vital to ensure maximum outcomes for this particularly vulnerable population.

Table 13: Comorbidities in Subjects who Died (Study EPOANE3021: Safety Analysis Set)

Treatment Group	Subject ID	Verbatim/ Preferred Term/ System Organ Class (RRC/IWG2006)	Erythroid Response	Comorbidities (ongoing medical history)
Age/Sex				**Deaths that occurred due to treatment-emergent events with onset in the first 24 weeks**
Epoetin Alfa	73/Male	Cachexia/ Cachexia/ Metabolism and nutrition disorders	No	gastritis, esophagitis, chronic atrial fibrillation, heart failure, osteoarthritis in both knee joints, benign prostatic hyperplasia, and secondary hemochromatosis.
	71/Female	Sudden death/ Sudden death/ General disorders and administration site conditions	No	cholelithiasis, pylorospasm, and Sheehan's syndrome (postpartum hypopituitarism)
	66/Male	Progressive AML/ Acute myeloid leukaemia/ Neoplasms benign, malignant and unspecified (incl cysts and polyps)	No	arthrosis left shoulder (osteoarthritis) and hypertension

	94/Male	Kidney insufficiency/ Renal failure/ Renal and urinary disorders	No	bradyarrhythmia, cardiac pacemaker insertion due to atrial arrhythmia, partial small intestinal resection, and compensated renal insufficiency
Placebo	75/Male	Evolution in AML/ Acute myeloid leukaemia/ Neoplasms benign, malignant and unspecified (incl cysts and polyps)	No	gastritis and gout,
Deaths that occurred due to treatment-emergent adverse events with onset after Week 24				
Epoetin Alfa	69/Female	Atypical progression with skin specific lesions Disease progression General disorders and administration site conditions	No	arterial hypertension, non-insulin dependent diabetes mellitus, dyslipemia, and hypothyroidism
	89/Male	Sudden death/ Sudden death/ General disorders and administration site conditions	Yes	arterial hypertension, benign prostatic hypertrophy, and cerebral atherosclerosis
	87/Male	Congestive heart failure/ Cardiac failure congestive/ Cardiac disorders	No	acute coronary syndrome, arterial hypertension, atrial fibrillation, carrier of femoral device (use of limb prosthesis), traumatic fracture, and villous adenoma of duodenal bulb

Note: Adverse events terms are coded using MedDRA/E version 14.0.
AML = acute myeloid leukemia; RRC = Response Review Committee
Source: initial application: CSR EPOANE3021/ Att LSIDTH01, Attachment Subject Narratives (Mod5.3.5.1).

In summary, elderly patients with comorbidities are a particularly vulnerable population. The Applicant recommends that the clinicians carefully evaluate the status of each patient, follow all the warnings and precautions in the proposed label for EPREX, as well as the guidelines endorsed by regional or country health authorities.

Assessor's comment

Among the 8 deaths, 4 subjects had cardiac/renal related comorbidities, 3 subjects had MDS disease progression and 1 subject had a sudden death with unclear cause. Due to the low number of deaths in the elderly population, no supplement recommendation could be propose. In the same way that the other indications, the MAH should add a warning in the section 4.2 of the SmPC to physicians "*Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a phycians's evaluation of the individual patient's clinical course and condition is necessary*".**Issue solved provided modification in section 4.2 of the SmPC proposed by the Rapporteur**

SMPC

QUESTION-17

The MAH should mention in section 5.1 that all of the responding subjects were in the strata with serum erythropoietin less than 200 mU/ml during screening.

In addition, please add for the EPO levels the units as mentioned in the International System of Units (comment).

APPLICANT RESPONSE

The Applicant added the following text (marked as double underline) for the content under the subsection "Treatment of adult patients with low- or intermediate-1-risk MDS" in the Section 5.1 of the proposed SmPC (Mod1.3.1/SmPC/Sec 5.1):

"Erythroid response was defined according to IWG 2006 criteria as a haemoglobin increase ≥ 1.5 g/dL from baseline or a reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline, and a response duration of at least 8 weeks. All of the responding subjects were in the stratum with serum erythropoietin less than 200 mU/ml during screening."

Assessor's comment

As requested by the CHMP, the MAH has mentioned in section 5.1 that all of the responding subjects were in the strata with serum erythropoietin less than 200 mU/ml during screening.

In addition, times to first transfusion were detailed in both group which is acceptable: "*Median time from baseline to first transfusion was statistically significantly longer in the epoetin alfa group compared to placebo (49 vs. 37 days; p=0.046)*".

Issue solved

QUESTION-18

The MAH should justify the (very short) dosing recommendations proposed for section 4.2, which cover only a part of the dosing recommendations used during the study (CSP section 6) and are thus considered insufficient and confusing, and align accordingly. (comment).

APPLICANT RESPONSE

Based on the Agency's comments, the Applicant has revised the dosing information in the label to include several key elements from the protocol in the dosing recommendations (Mod1.3.1/SmPC/Sec 4.2). Additional dosing related discussions and justifications can be found in Applicant's response to Question-2.

For the purpose of clarity, the proposed revised dosing information in the EPREX SmPC is displayed below side-by-side with the dosing of the EPOANE3021 study protocol in Table 14.

In addition, the revised information related to dosing is provided in "Track Changes" mode below in comparison with the initially proposed dosing in the EPREX SmPC that was submitted on 24 March 2016. Deletion is marked as strikethrough and addition is marked as double underline.

Table 14: Comparison of Dosing Information between the Proposed EPREX SmPC and the EPOANE3021 Study Protocol

<table>
<tr><th>PROTOCOL</th><th>Revised PROPOSED SmPC</th></tr>
<tr><td>
• Starting dose of 450 IU/kg (max total dose of 40,000 IU)
• Erythroid response assessed at Week 8 (IWG 2006 criteria) ○ If no Erythroid response and hemoglobin below 11 g/dL increase dose from 450 IU/kg to 1050 IU/kg once every week
○ If no Erythroid response and hemoglobin above 11 g/dL increase dose from 450 IU/kg to 787.5 IU/kg once every week
• Dose escalation during the first 8 weeks and dose escalation above 1050 IU/kg are not allowed
• Maximum total drug allowed is 40,000 IU once every week for the first 8 weeks and 80,000 IU once every week at any other time
• Stepwise dose reduction allowed any time
• If no Erythroid response while receiving maximum dose for at least 4 weeks then subject withdrawn from study
• If dose escalation indicated after dose reduction, minimum of 4 weeks should elapse between repeated dose increases
• Adjust dose if hemoglobin
○ exceeds 12 g/dL
○ increases by more than 2 g/dL over any 4 week period ○
<table>
<tr><th>Hemoglobin Criteria*</th><th>Dose Adjustment</th></tr>
<tr><td>Hb >12g/dL</td><td>Withhold dose until Hb <11g/dL., then reduce dose by 1 step and restart.</td></tr>
<tr><td>Hb increases by >2 g/dL over any 4week period</td><td>Reduce dose by 1 step and administer as scheduled.</td></tr>
<tr><td>HC decreases by ≥1g/dL after dose reduction</td><td>Increase dose by 1 step to previous dose and administer as scheduled. Allow minimum of 4 weeks between repeated dose increases.</td></tr>
<tr><td colspan="2">*Hb assessments based on untransfused hemoglobin</td></tr>
</table>
decreases by at least 1 g/dL after dose reduction
(table above a summary of the protocol table)
• All dose adjustments must be done in single steps based on subject's
</td><td>
EPREX, ERYPO should be administered to patients with symptomatic anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

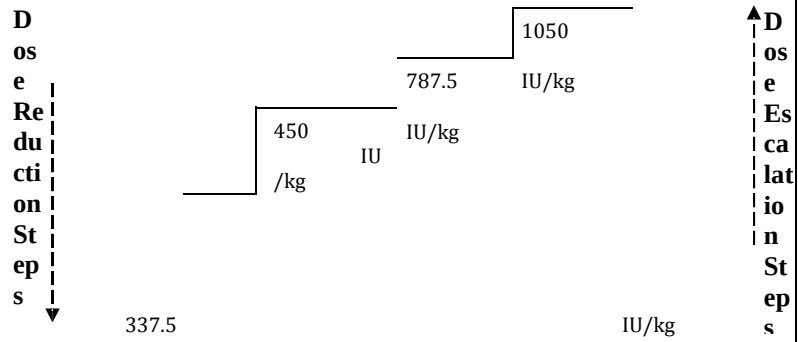
The recommended starting dose is EPREX, ERYPO 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week with not less than 5 days between doses.

~~It is recommended that response be assessed at week 8. If no erythroid response is achieved after 8 weeks according to IWG 2006 criteria (see section 5.1 *Pharmacodynamic properties – Clinical efficacy and safety*), and the haemoglobin concentration is below 11 g/dL (6.8 mmol/L), the dose should be increased from 450 IU/kg once every week to 1050 IU/kg once every week (maximum dose is 80,000 IU per week).~~

Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). ~~See diagram below for guidelines for stepwise dose adjustment. Epoetin alfa should be withheld or the dose reduced when the haemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Upon dose reduction, if haemoglobin concentration drops ≥1g/dL the dose should be increased.~~It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time (see diagram below). A haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.

Dose increase: Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week. If the patient loses response or haemoglobin concentration drops by ≥1 g/dL upon dose reduction the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between repeated dose increases.

Dose hold and decrease: Epoetin alfa should be withheld when the haemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Once the haemoglobin level is <11g/dL, the dose can be restarted on the same dosing step or one dosing step down based on physician judgment.
</td></tr>
</table>

current dose	Decreasing the dose by one dosing step should be considered if there is a rapid increase in haemoglobin (>2 g/dL over 4 weeks).  ~~A sustained haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.~~

Assessor's comment

The revised SmPC proposed by the MAH is acceptable.

Issue solved

QUESTION-19

There were 4 (4.7%) subjects in the epoetin alfa group with TVEs (sudden death, ischemic stroke, embolism [distal deep venous thrombosis], and phlebitis [distal deep venous thrombosis]); all TVEs occurred during the first 24 weeks of the study. These higher rate should be mentioned in the section 5.1 of the SmPC.

APPLICANT RESPONSE

Based on the Agency's comments, the Applicant added the following content (marked as double underline) under the subsection "Treatment of adult patients with low- or intermediate-1-risk MDS" in the Section 5.1 of the proposed SmPC (Mod1.3.1/SmPC/Sec 5.1):

> *There were 4 (4.7%) subjects with TVEs (sudden death, ischemic stroke, embolism, and phlebitis). All TVEs occurred in the epoetin alfa group and in the first 24 weeks of the study. Three were confirmed TVE and in the remaining case (sudden death), the thromboembolic event was not confirmed. Two subjects had significant risk factors (atrial fibrillation, heart failure and thrombophlebitis).*

Assessor's comment

The RMS agrees with these supplement safety data in section 5.1 of the SmPC.

Issue solved

QUESTION-20

According to the MAH, there is no new safety signal. The most common treatment emergent adverse events during the first 24 weeks that were reported more frequently (>2% higher) in the epoetin alfa group than in the placebo group were asthenia, fatigue, nasopharyngitis, diarrhea, dyspnea, constipation, and pruritis. Therefore, SmPC section 4.8 should be updated with new data from pivotal study EPOANE3021, i.e. including information about patients treated for MDS in the introductory paragraph "Of a total 3,262 subjects in 23 randomised,… studies,…" and any further concerned paragraph. (comments).

In addition, the MAH is requested to adapt the tabular format of undesirable effects as follows:

MedDRA system organ classification (SOC)	Adverse Reaction (Preferred Term Level)	Frequencies

believes that this tabular format is more clear (supported by).

APPLICANT RESPONSE

Based on the Agency's comments, the Applicant has revised the content under the subheading "Tabulated List of Adverse Reactions" in Section 4.8 of the initially proposed SmPC (Mod1.3.1/SmPC/Sec 4.8) to include the safety information from 2 studies conducted by the Applicant in subjects with low- or intermediate-1-risk MDS (EPOANE3021 and the EPO-ANE-3018 studies). The changes are provided in "track changes" mode below in comparison with the initially proposed information in the EPREX SmPC that was submitted on 24 March 2016. Deletion is marked as strikethrough and addition is marked as double underline.

Of a total ~~3,262~~3,417 subjects in ~~23~~ 25 randomized, double-blinded, placebo or standard of care controlled studies, the overall safety profile of EPREX was evaluated in ~~1,992~~2,094 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]; 1,404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; ~~and~~213 exposed subjects in 1 study in the perisurgical period; and 102 exposed subjects in 2 MDS studies.

In addition, the Applicant has generated a revised table in the tabular format as requested by the Agency for undesirable effects in Section 4.8 of the proposed SmPC (Mod1.3.1/SmPC/Sec 4.8).

Assessor's comment

The MAH has updated the section 4.8 with the new safety date from EPOANE3021 and 3018 studies.

Issue solved

QUESTION-21

The MAH is requested to cite the name and the number of all the studies reporting in the section 5.1. (comment).

APPLICANT RESPONSE

Regarding the request to cite the name and number of all the studies reported in Section 5.1, the Applicant proposes to implement this request with the next SmPC related variation which will be submitted before July 2017.

Assessor's comment

The RMS agrees with the MAH to update the section 5.1 with the name and number of all the studies reported in the next SmPC submitted brfore July 2017.

Issue solved

QUESTION-22

Section 5.2: In the section upon pediatric population the MAH is requested to specify name and number of the study. Moreover the MAH is requested to clarify if the study in this section is the K90-033 study. In this case the MAH is request to discuss and clarify the discrepancies in the number of subjects reported in SPC (7 preterms newborn) from that reported in the study itself (8 preterms newborn) (comments).

APPLICANT RESPONSE

The study mentioned in Section 5.2 was published in 1996 in J Appl Physiol by Widness JA et al (Widness 1996)[23] and is not the K90-033 study. In this study, 7 preterms newborn were included. This pharmacokinetic (PK) study and the wording in Section 5.2 were discussed more fully during the paediatric worksharing procedure (UK/WS/026/pd/WS/001) that was concluded in October 2015, and the SmPC wording was implemented by MRP Variation FR/H/003/09-10, 13-14/IB/123, and approved in February 2016.

Assessor's comment

The MAH provided supplement information concerning section 5.2 as requested by the CMDH.

Issue solved

QUESTION-23

Finally, responses submitted to the Medical products Agency should contain product information also in Word format. Proposed changes should be shown as tracked changes. (comment).

APPLICANT RESPONSE

The Applicant will provide the product information (ie, SmPC) in the current submission with the format requested by the Agency.

Assessor's comment **Issue solved**

DATA NOTIFICATION AND CORRECTION

During the preparation of the response to Agencies, the Applicant has been made aware of 2 data related issues. Although these issues do not change the overall study outcome and conclusions, the Applicant would like to openly disclose them to the Agencies and address them transparently during this submission.

1. CHANGES REGARDING STRATIFICATION FACTORS

Following issuance of the final CSR, it became evident that the transfusion requirement data used for the stratification were from the IVRS-indicated data rather than the actual data recorded in the CRF. (the serum erythropoietin levels used for stratification were the CRF-recorded values per the statistical analysis plan).

This error has been corrected in a CSR Erratum included in this submission (Mod5.3.5.1/EPOANE3021 CSR Erratum). A representative of key changes for the erythroid response by stratification group in Table 12 of the initial CSR is displayed in Table 15 (in "track changes" mode: deletion marked as strikethrough and addition marked as double underline).

Table 15: Erythroid Response at Any Time During the First 24 Weeks (Study EPOANE3021: Modified Intent-to-Treat Analysis Set)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Subjects with erythroid response[a] at any time during the first 24 weeks of study	2 (4.4%)	27 (31.8%)
p-value [b]		<0.001
Subjects with erythroid response by stratification group		
Strata 1: Transfusion="No" and serum erythropoietin level less than 200 mU/mL[c]	1 (~~5.0~~4.8%)	~~18~~ 20 (~~47.4~~ 50.0%)
Strata 2: Transfusion="Yes" and serum erythropoietin level less than 200 mU/mL[c]	1 (~~5.3~~5.6%)	~~9~~ 7 (~~27.3~~ 22.6%)
Strata 3: Transfusion="No" and serum erythropoietin level at least 200 mU/mL	0	0
Strata 4: Transfusion="Yes" and serum erythropoietin level at least 200 mU/mL	0	0
p-value[d]		<0.001
Subjects with erythroid response by IPSS risk category		
Low = 0[e]	2 (8.7%)	16 (45.7%)
Intermediate-1 = 0.5 to 1.0[e]	0	10 (20.4%)
Intermediate-2 = 1.5 to 2.0	0	0
High = ≥2.5	0	0
No IPSS at screening	0	1
p-value[d]		<0.001
Percentage of subjects with erythroid response at any time during the first 24 weeks of study for evaluable subjects[f]	2 (4.4%)	27 (32.9%)

[a] Erythroid response determined by the RRC according to the IWG 2006 criteria: Hemoglobin increase by ≥1.5 g/dL or relevant reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared with the pretreatment transfusion number in the previous 8 weeks; responses must last at least 8 weeks.

[b] p-value for treatment group differences are based on the Fisher exact test, 2-sided.

[c] The CMH p-value and percentages are based on the number of subjects in that strata: placebo, Strata 1 = ~~20~~ 21and Strata 2 = ~~19~~ 18; epoetin alfa, Strata 1 = ~~38~~ 40 and Strata 2 = ~~33~~ 31.

[d] p-value for treatment group differences are based on the CMH test, 2-sided.

[e] The CMH p-value and percentages are based on the number of subjects in that IPSS category: placebo, Low 0 = 23 and Intermediate-1 = 22; epoetin alfa, Low 0 = 35 and Intermediate-1 = 49.

[f] The denominator excludes subjects who were determined by the RRC as not evaluable.

CMH = Cochran-Mantel-Haenszel; IPSS = International Prognostic Scoring Systems; IWG = International Working Group; RBC = red blood cell; RRC = Response Review Committee.

Source: ~~Attachment TEFER01a~~ initial application: CSR EPOANE3021/Att. TEFER01a (Mod5.3.5.1); Mod5.3.5.1/EPOANE3021 CSR Erratum.

Assessor's comment

These issues do not change the overall study outcome and conclusions which is acceptable.

2. CHANGES REGARDING DURATION OF ERYTHROID RESPONSE BASED

V.1 ON RESPONSE REVIEW COMMITTEE ASSESSMENT

After issuance of the final CSR, a discrepancy was noted between the reported end of response (reported as Week 23) and the documented response at Week 24 (reported as a responder at Week 24) for one subject. To address this discrepancy, the case was re-submitted to the RRC for re-review, in the same blinded manner as the initial review. The RRC confirmed that the subject was a responder at Week 24 and the end of the response was corrected to Week 25.

This error has been corrected in a CSR Erratum included in this submission (Mod5.3.5.1/EPOANE3021 CSR Erratum). A representative of key changes for the duration of erythroid response in the attachment table TEFDUR01a in the initial CSR is displayed in Table 16 (in "track changes" mode: deletion marked as strikethrough and addition marked as double underline).

Table 16: **Revised TEFDUR01a: Duration of Erythroid Response;**
Modified Intent-to-Treat Analysis Set (Study EPOANE3021)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat	45	85
Duration of erythroid response (days) at any time during first 24 week [a] [b]		
N	2	27
Mean (SD)	99.0 (69.30)	192.~~3~~8 (88.~~9~~275)
Median	99.0	197.0
Range	(50 , 148)	(54 , 323)
(Lower 95% CI, Upper 95% CI for the Mean)	(-523.6 , 721.6)	(157.~~1~~7, 227.~~5~~9)

[a] Duration of Erythroid Response determined by the Response Review Committee (RRC) defined as the number of days from (date of ending week response - date of starting week response + 1). [b] Duration for subjects that have met the IWG criteria including the 8 weeks duration requirement in the first 24 weeks but it can extend also after W24.

Source: ~~Attachment TEFDUR01a~~ initial application: CSR EPOANE3021/ Att TEFDUR01a (Mod.5.3.5.1); Mod5.3.5.1/EPOANE3021 CSR Erratum.

Assessor's comment

These issues do not change the overall study outcome and conclusions which is acceptable.

VII. FURTHER REQUESTS ASKED TO THE MAH AND ASSESSMENT OF THE RESPONSES

QUESTION 1 ( )

A supplement warning should be added in the section 4.2 of the SmPC to physicians "Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary"

APPLICANT RESPONSE

This warning has been added to section 4.2 of the SmPC (See EUPI).

Assessor's comment **Issue solved**

QUESTION 2 ()

Section 5.1:

In the 2nd paragraph, the description of baseline erythropoietin should be reworded from "less than 200 mU/mL" to "< 200 mU/mL" for easiness of understanding. (from Q17)

The last new paragraph about TVE does not contain any efficacy information but only safety information. It should be placed in section 4.8 (and/or section 4.4) instead. (from Q19)

APPLICANT RESPONSE

In the SmPC,

- "Less than 200 mU/mL" has been changed to "<200 mU/mL"
- The information on TVE proposed in Section 5.1 has been moved to Section 4.8

Assessor's comment **Issue solved**

QUESTION 3 ( )

PL section 4:

The listing of adverse reactions need to be updated to be in line with section 4.8.

APPLICANT RESPONSE

The package leaflet has been adjusted accordingly (See EUPI).

Assessor's comment **Issue solved**

QUESTION 4 ()

(Question 11, originally proposed by , not considered fully resolved by)

1. The treatment effect of Eprex in patients with prior transfusions is lower than in patients without. Further, few patients reached a response based on RBC transfusion decrease. The treatment effect within this group needs further clarification and discussion for patients with sEPO<200 mU/ml (current indication). The following points need to be taken into account:

• Number of patients with baseline transfusion less than 2 RBC units and between 2 and 4 units in 8 weeks prior to baseline visit, and between week 16 and week 24.

• Overall % of patients reaching the primary endpoint and number of patients reaching a response based on RBC transfusion decrease.

• Need for RBC transfusions during follow-up. The impact on need for transfusions during follow-up should be discussed in relation to the criterion for RBC transfusion decrease within the primary endpoint.

• Safety data in patients with sEPO level <200 mU/ml receiving transfusions before randomization (n=33) and in patients independent of transfusions (n=38) in order to compare the safety profile in these two population.

In addition, outcome data need to be presented separately for patients with and without prior transfusions within section 5.1 of the SmPC (see comments on SmPC).

<u>Rationale</u>

An integral discussion of the treatment effect of Eprex in patients with transfusions prior to baseline is needed as efficacy is lower and the impact on reduction in RBC transfusion is not entirely clear. Exact data need to be presented for patients included in the revised indication, i.e. sEPO<200 mU/ml.

APPLICANT RESPONSE

The Applicant would like to provide responses to this question in 3 Parts.

PART-1

The Agency asked for further clarification and discussion of the treatment effect in subjects with sEPO <200 mU/mL with or without prior transfusion (see below in bold) The treatment effect of Eprex in patients with prior transfusions is lower than in patients without. Further, few patients reached a response based on RBC transfusion decrease. The treatment effect within this group needs further clarification and discussion for patients with sEPO<200 mU/ml (current indication).

APPLICANT RESPONSE

To address the Agency's request, a series of analyses were performed focused on subjects in the epoetin alfa group with regards to their transfusion status and baseline sEPO <200 mU/mL.
The subject distribution according to the 2 stratification factors (with or without prior transfusions and sEPO ≥ or <200 mU/mL) is provided in the Table below.

Table 1: Subjects in the Epoetin Alfa Group Stratified by Baseline sEPO Level and the Baseline Transfusion Status			
	Without Prior Transfusions[a] N (%)	With Prior Transfusions[a] N (%)	Overall N (%) 85=100%
All subjects	41 (48.2%)	43 (50.6%)	84[b] (98.8%)
sEPO ≥200 mU/ml	1 (1.2%)	12 (14.1%)	13 (15.3%)
sEPO <200 mU/ml	40 (47.1%)	31 (36.5%)	71 (83.5%)
[a]: During 8 weeks prior to the baseline visit [b] One subject in the epoetin alfa group did not have sEPO data			

The results showed that in the epoetin alfa group, majority of subjects (83.5%) had baseline sEPO level <200 mU/mL. Among them, 47.1% of subjects did not receive transfusion and 36.5% of subjects received transfusion during the 8 weeks prior to the baseline visit.

The treatment effect, ie, the erythroid response, within the epoetin alfa group analysed according to responder's baseline sEPO level and their baseline transfusion status is provided in Table below.

Table 2: Subjects with Erythroid Response[a] in the Epoetin Alfa Group Stratified by Baseline sEPO Level and the Baseline Transfusion Status			
	Without Prior Transfusions[b] N (Response%)	**With Prior Transfusions[b] N (Response%)**	**Overall N (Response%)**
All subjects	20/41 (48.8%)	7/43 (16.3%)	27/85[e] (31.8%)
sEPO ≥200 mU/ml	0/1	0/12	0/13
sEPO <200 mU/ml	20/40 (50.0%) all by Hb[c] measurement	7/31 (22.6%) Hb[c]: 5/31 (16.1%) Tf[d]: 2/31 (6.5%)	27/71 (38.0%) Hb[c]: 25/71 (35.2%) Tf[d]: 2/71 (2.8%)
[a] Definition of erythroid response was according to IWG2006 and assessed by an independent Response Review Committee. [b] During 8 weeks prior to the baseline visit [c] Hb level pretreatment <11 g/dL, and after treatment increase by ≥1.5 g/dL for at least ≥8 weeks. [d] Two subjects reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline [e] One subject in the epoetin alfa group did not have sEPO data			

The results showed that in the epoetin alfa group,

- All responders had baseline sEPO level <200 mU/mL (as indicated before).
- Among subjects with sEPO <200 mU/mL, subjects without prior transfusion showed

- higher ER rate than those with prior transfusion (50.0% vs. 22.6%).
- Among all the responders, majority of the responses were determined by the Hb increase according to the IWG2006 criteria (25 of 27 responders). Only 2 subjects' responses were based on the transfusion reduction according to the IWG2006 criteria. Both subjects were noted to have 4 units of RBC transfusion during the 8 weeks prior to the baseline visit (for details, see Table 8 and Table 10 in the MRP response document submitted to the RMS on 07 October 2016).

PART-2

The Agency raised 4 specific points in the comment. The Applicant wishes to address the 4 points in Agency's comments below point by point.

Please note that all analyses below are focused on subjects who were in the epoetin alfa group with baseline sEPO <200 mU/mL.

Point-1

 Number of patients with baseline transfusion less than 2 RBC units and between 2 and 4 units in 8 weeks prior to baseline visit, and between week 16 and week 24.

APPLICANT RESPONSE

For analyzing the data, the Applicant made the following assumptions:
 the term "transfusion less than 2 RBC units" includes subjects with transfusion units of 1 and 2
 the term "transfusion between 2 and 4 units" includes subjects with transfusion units of 3 and 4.

The analysis data for transfusion during an 8-week period as requested are summarized in the Table below. Detailed information for each subject who received transfusion during the Weeks 16 to 24 is provided in Attachment 1

Table 3: The Number of Subjects According to Transfusion Units Received in the Epoetin Alfa Group with sEPO <200 mU/mL

Transfusion Time	The Number of Subjects According to Transfusion Units Received		
Transfusion Units	**1-2 U**	**≥3 U**	**total**
In 8 Weeks prior to the baseline visit	16 (51.6%)	15 (48.4%)	31 (100%)
In Weeks 16 to 24	6 (46.2%)	7 (53.8%)	13 (100%)

The results showed that among subjects in the epoetin alfa group with sEPO <200 mU/mL who received transfusion prior to baseline, 41.9% (13 of 31) subjects received transfusion in Weeks 16 to 24. The distribution in degree of RBC transfusion need (1-2 Units vs ≥3 Units) was similar between the baseline and the Weeks 16 to 24 in this subset of study population.

Point-2

 Overall % of patients reaching the primary endpoint and number of patients reaching a response based on RBC transfusion decrease.

APPLICANT RESPONSE
The overall percentage of subjects treated with epoetin alfa reached the primary efficacy endpoint was 31.8% (27 of 85), and among the 27 subjects, 2 subjects (7.4%) reached the primary efficacy endpoint based on RBC transfusion decrease criterion outlined by IWG2006. More detailed data for these 2 subjects and related discussions were also provided in the responses to MRP Question-9 and Question-12, as well as in Table 10 of the response document submitted to the RMS on 07 October 2016.

Point-3
 Need for RBC transfusions during follow-up. The impact on need for transfusions during follow-up should be discussed in relation to the criterion for RBC transfusion decrease within the primary endpoint.

APPLICANT RESPONSE
The Applicant interprets the term "during follow-up" as the period between Week 24 and Week 48 in the EPOANE3021 study. Please note that at Week 24, only 39 subjects who were responders assessed by the investigators continued to the treatment extension phase.

The analysis data for transfusion during a 24-week period as requested are summarized in the Table below. Detailed information for each responder who received transfusion during the Weeks 1 to 24 is provided in Table 8 of the MRP response document submitted to the RMS on 07 October 2016. Detailed information for each subject (including the responders) who received transfusion during the Weeks 24 to 48 is provided in Attachment 2.

Table 4: The Number of Subjects According to Transfusion Units Received in the Epoetin Alfa Group with sEPO <200 mU/mL

Transfusion Time	The Number of Subjects According to Transfusion Units Received		
Transfusion Units	1-2 U	≥3 U	total
Subject with Transfusion in Weeks 1 to 24	16	15	31
Responders in Subject with Transfusion during the first 24 Weeks	5 (31.3%)	2 (13.3%)	7 (22.6%)
Subject with Transfusion in Weeks 24 to 48	9	5	14
Responders in Subject with Transfusion in Weeks 24 to 48	1 (11.1%)	1 (20%)	2 (14.3%)

Two subjects had ER and received transfusions during Weeks 24 to 48. One of the responders received transfusions due to blood loss after a surgery [a reason other than (strictly) anemia], and the other responder received transfusions prior to baseline, and met the IWG2006 criteria based on the transfusion reduction (see Attachment 2).

Point-4

 Safety data in patients with sEPO level <200 mU/ml receiving transfusions before randomization (n=33) and in patients independent of transfusions (n=38) in order to compare the safety profile in these two population.

APPLICANT RESPONSE

A series of safety analyses were performed for subjects in the epoetin alfa group with baseline sEPO <200 mU/mL according to their baseline status of transfusion. A summary table for key safety findings of these subjects is provided below.

Table 5: Summary of Key Safety Findings for Subjects in the Epoetin Alfa Group with sEPO <200 mU/mL by Baseline Transfusion Status (Study EPOANE3021: Safety Analysis Set)

	With Prior Transfusion[a]	Without Prior Transfusion[a]
Analysis set: safety and serum EPO <200mU/mL - treatment phase only	31	40
Subjects reporting:		
At least 1 treatment-emergent adverse event	23 (74.2%)	32 (80.0%)
At least 1 treatment-emergent serious adverse event	9 (29.0%)	10 (25.0%)
At least 1 thrombotic vascular event	2 (6.5%)	1 (2.5%)
Disease progression[b]	7 (22.6%)	4 (10.0%)

[a]. During 8 weeks prior to the baseline visit.
[b] Disease progression is defined as according to the International Working Group (IWG) Response Criteria 2006.
Source: TSFAE01d1, TSFAE03d1, TSFTVE021, TSFREL021.

Detailed data of safety analyses (see list below) are provided in the Attachments (see laboratory responses document).

The analyses showed that the overall rates of TEAEs/TESAEs were generally similar between groups with the exception of disease progression, which seemed higher in subjects with prior transfusion. As shown in the attachment tables, no other meaningful conclusions can be made because of the relatively low number of individual events.

In addition, the Applicant would like to point out that the number of subjects with sEPO level <200 mU/mL with or without baseline transfusion in the safety analyses discussed here are slightly different from the numbers in the original CSR cited by the Agency in the comment (ie, with transfusion: n=31 [instead of 33]; without transfusion: n=40 [instead of 38]). The reason for this correction was indicated in the last Section "Data Notification and Correction" of the Applicant's MRP response document submitted to the RMS on 07 October 2016, and the details are also provided in the "EPOANE3021 CSR Erratum" report that was included in the same submission.

PART-3

The Agency commented on outcome data presentation in Section 5.1 of the SmPC (see bold below)

In addition, outcome data need to be presented separately for patients with and without prior transfusions within section 5.1 of the SmPC (see comments on SmPC).

APPLICANT RESPONSE
This comment has been addressed in Applicant Response to Question 6 in this document and in the SmPC (See SmPC for proposed revisions).

Assessor's comment
Issue solved

QUESTION 5 ( ) *(Question 6, not considered fully resolved)*
2. The applicant should provide additional data in support of their statement that the primary outcome was not affected by the heterogeneity in Hb measurements. Responder rates should be presented for patients for which the Hb measurement was performed in the same way throughout the 24 weeks and for those with varying Hb collections (hospital lab, local lab, hemophotometer, etc.). Any discrepancies and their impact on the primary efficacy outcomes should be discussed.

Rationale
Data are considered needed as it concerns the primary efficacy outcome and these can be easily presented by the applicant to support their statement that the type of Hb measurements did not impact the primary outcome.

APPLICANT RESPONSE
Throughout the study EPOANE3021 (treatment phase and treatment extension phase), Hb was measured every week, either at the study center or by a Home Health Care Professional, to guide treatment. Subjects returned to the study center every 4 weeks. If Hb was measured outside the study center by a Home Health Care Professional, the investigator reviewed the measurement to adjust the dose of study drug, where required.

For further analyses of erythroid responses according to how the Hb measurement data were determined, 2 analyses were performed:
(1) "Across All Measures Over 24 Weeks" - In this analysis, all weekly Hb measures were taken into account;
(2) "Across Only Monthly Measures Over 24 Weeks" - In this analysis, only the Hb measurements performed during the subject's monthly visit to the study center were taken into account (ie, the baseline visit, and visits every 4 weeks thereafter until the Week 24).

The results for both analyses in subjects with baseline sEPO <200 mU/mL are shown in Table below.

Table 6 (TEFER01a2): Erythroid Response at any Time During the First 24 Weeks by Lab Consistency Status During Study for Subjects with Serum Erythropoietin Level Less than 200 mU/mL at Screening; Modified Intent-to-Treat Analysis Set (Study EPOANE3021)

	Placebo	Epoetin Alfa
Analysis set: modified intent-to-treat and serum EPO <200mU/ml	39	71
Subjects with erythroid response [a] at any time during the first 24 Weeks of study	2 (5.1%)	27 (38.0%)
Across All Measures Over 24 Weeks		
Hemoglobin (Hb) Measured at Same Lab		
N	21	29
Subjects with erythroid response [a] at any time during the first 24 Weeks of study	0	9 (31.0%)
Hemoglobin (Hb) Measured at Different Labs or With Hemophotometer		
N	18	42
Subjects with erythroid response [a] at any time during the first 24 Weeks of study	2 (11.1%)	18 (42.9%)
Across Only Monthly Measures Over 24 Weeks		
Hemoglobin (Hb) Measured at Same Lab		
N	32	52
Subjects with erythroid response [a] at any time during the first 24 Weeks of study	1 (3.1%)	19 (36.5%)
Hemoglobin (Hb) Measured at Different Labs or With Hemophotometer		
N	7	19
Subjects with erythroid response [a] at any time during the first 24 Weeks of study	1 (14.3%)	8 (42.1%)

[a] Erythroid Response determined by the Response Review Committee (RRC) according to the IWG 2006 criteria: Hb increase by ≥1.5 g/dL or relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks and lasting at least 8 weeks.

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The results in the epoetin alfa group showed:

 In the analysis of "Across All Measures Over 24 Weeks" (where all weekly Hb measures were taken into account), there were 29 of 71 (40.8%) subjects with Hb measures performed by the same lab. Among the 29 subjects, 9 (31.0%) met the IWG2006 ER criteria. There were 42 of 71 (59.2%) subjects who had at least 1 Hb measurement done by a different lab. Of the 42 subjects, 18 (42.9%) met the IWG2006 ER criteria.

Please note that it was allowed in the study to measure Hb in the home setting with hemophotometers, especially for elderly subjects.

 In the analysis of "Across Only Monthly Measures Over 24 Weeks" (where only the Hb measurements performed during the subject's monthly visit to the study center were taken into account), there were 52 of 71 (73.2%) subjects with Hb measures performed by the same lab. Among the 52 subjects, 19 (36.5%) met the IWG2006 ER criteria. There were 19 of 71 (26.8%)

subjects who had at least 1 Hb measurement done by a different lab. Of the 19 subjects, 8 (42.1%) met the IWG2006 ER criteria.

Please note that it was allowed in the study for the study center to work with different labs.

Overall, the 2 analyses showed similar results with respect to the distribution of ER. A higher percentage of responders were observed in subjects with at least one different lab measuring the Hb value. The Applicant would like to point out that because of the complexity in assessing the ER, the RRC was commissioned in the study. During the RRC review, the sources of Hb values for each subject were clearly indicated.

Assessor's comment

Issue solved

QUESTION 6 ( )
Other concerns not already raised by
Section 5.1:
Baseline characteristics of the patient population with regard to sEPO (<200 mU/ml or ≥200 mU/ml), Hb (mean, range) and prior transfusions (yes/no, ≤ 2 RBC units and > 2 and ≤ 4 RBC units) should be included in the description of the study population to characterize the patient population in the study. Results concerning transfusions between Week 16 and Week 24 could also be included (if they are relevant).
Efficacy outcomes should be presented stratified for sEPO and patients with and without prior transfusions, including the type of response (Hb increase or decrease in RBC transfusions). A tabular presentation is preferred, in line with the suggestion below.

Patients with erythroid response* during the first 24 weeks of Eprex treatment

	Without prior transfusions N= (%)	With prior transfusions N= (%)	Overall N= (%)
All patients			
sEPO > 200 mU/ml			
sEPO < 200 mU/ml		**	

*** Definition of erythroid response**
**** n= patients reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline**

Rationale
sEPO, Hb and prior transfusions are important factors that affect response to ESA treatment and the response rate substantially differs based on sEPO and prior transfusions.

APPLICANT RESPONSE
Baseline Characteristics of the Study Population
The key baseline characteristics of the study population with regard to sEPO (<200 mU/mL), Hb (mean, range) and prior transfusions (yes/no, ≤ 2 RBC units and > 2 and ≤ 4 RBC units) are provided in the Table below. Please note that the analyses for baseline Hb level and transfusion

status are focused on subjects with baseline sEPO <200 mU/mL, since this is the SmPC intended target patient population.

Table 7 (TSIDEM011): Key Baseline Characteristics in Subjects with sEPO <200 at Screening;
(Subset of Full Analysis Set)

	Placebo	Epoetin Alfa	Total
Total	45	85[a]	130
Analysis set: serum EPO ≥200 mU/mL	6	13	19
Analysis set: serum EPO <200mU/mL	39	71	110
Below: Analysis set: serum EPO <200mU/mL			
Hemoglobin (g/L)			
N	39	71	110
Mean (SD)	92.1 (8.51)	92.1 (8.57)	92.1 (8.51)
Median	96.0	94.0	94.0
Range	(69, 105)	(71, 109)	(69, 109)
(Lower 95% CI, Upper 95% CI for the Mean)	(89.3, 94.9)	(90.1, 94.1)	(90.5, 93.7)
Prior Transfusions			
N	39	71	110
Yes	17 (43.6%)	31 (43.7%)	48 (43.6%)
<= 2 RBC Units	9 (52.9%)	16 (51.6%)	25 (52.1%)
> 2 and <= 4 RBC Units	8 (47.1%)	14 (45.2%)	22 (45.8%)
> 4 RBC Units	0	1 (3.2%)	1 (2.1%)
No	22 (56.4%)	40 (56.3%)	62 (56.4%)

[a] One subject in the epoetin alfa group did not have sEPO data

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Additional analyses of medical history, demographics and baseline characteristics are also performed in subjects with baseline sEPO <200 mU/mL (see List below) and results are provided in the Attachments Section of the laboratory responses document:

Overall, the results showed that demographics and the baseline characteristics in subjects with sEPO<200 mU are similar to those in the entire study population (see Table 5 of the EPOANE3021 CSR). This finding is not surprising, since subjects with baseline sEPO <200 mU/mL represented a majority (83.5%) of the study population in the epoetin alfa group.

The results of key baseline characteristics of the study population are also included in the revised SmPC (See EUPI).
With respect to the results concerning transfusions between Week 16 and Week 24 (displayed in Table 3 in this document), the Table 3 showed that among subjects in the epoetin alfa group with sEPO <200 mU/mL who received transfusion prior to baseline, 41.9% (13 of 31) subjects received transfusion in Weeks 16 to 24. The distribution in degree of RBC transfusion need (1-2 Units vs ≥3 Units) was similar between the baseline and the Weeks 16 to 24 in this subset of study population.

Efficacy Outcome
The primary efficacy outcome (erythroid response) information in the requested format has been provided in the Table 2 in this document, and is displayed again in the Table below for the convenience of this review.

Table 8: Subjects with erythroid response[a] during the first 24 weeks of Eprex treatment

	Without Prior Transfusions[b] N (Response%)	With Prior Transfusions[b] N (Response%)	Overall N (Response%)
All subjects	20/41 (48.8%)	7/43 (16.3%)	27/85[e] (31.8%)
sEPO ≥200 mU/mL	0/1	0/12	0/13
sEPO <200 mU/mL	20/40 (50.0%) all by Hb[c] measurement	7/31 (22.6%) Hb[c]: 5/31 (16.1%) Tf[d]: 2/31 (6.5%)	27/71 (38.0%)

[a] Definition of erythroid response was according to IWG2006 and assessed by an independent Response Review Committee.
[b] During 8 weeks prior to the baseline visit
[c] Hb level pretreatment <11 g/dL, and after treatment increase by ≥1.5 g/dL for at least ≥8 weeks.
[d] Two subjects reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline
[e] One subject in the epoetin alfa group did not have sEPO data

The Applicant proposes to not include the information for subjects with sEPO ≥200 mU/mL from the table above in Section 5.1 of the SmPC, based on following reasons: (1) there were no responders in subjects with baseline sEPO ≥200 mU/mL, (2) there was only very small number of subjects in this subcategory, and (3) the proposed SmPC indication is intended to target patients with sEPO <200 mU/mL. (See SmPC for proposed revisions).

General Comment from the Applicant

As can be seen from the updated SmPC, the inclusion of the table (baseline characteristics and erythroid response) to Section 5.1 of the SmPC does not seem to provide added value to the information already proposed. It is the only table in Section 5.1 and as such stands out and yet does not add much to the already existing text on MDS. The Applicant would therefore prefer to delete the table from the EUPI.

Assessor's comment

Issue solved