SYNOPSIS

Name of Sponsor/Company	Janssen EMEA Medical Affairs*
Name of Investigational Product	JNJ-7472179 epoetin alfa

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Status: Approved

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Prepared by: Janssen-Cilag International N.V.

Protocol No.: EPOANE3021

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating Epoetin Alfa Versus Placebo in Anemic Patients With IPSS Low- or Intermediate-1-Risk Myelodysplastic Syndromes

EudraCT Number: 2010-022884-36

NCT No.: NCT01381809

Clinical Registry No.: CR018367

Coordinating Investigator(s): [redacted] MD - [redacted] France

Study Centers: The following include the number of centers in each country that screened or enrolled subjects: Bulgaria (5 centers); France (7 centers); Germany (7 centers); Greece (5 centers); Italy (12 centers); Russian Federation (2 centers)

Publication (Reference): None

Study Period: 29 September 2011 (first informed consent) to 06 January 2015 (last observation for last subject); Database lock: 23 September 2015

Phase of Development: 3

Objectives: 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 red blood cell [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 International Prognostic Scoring System (IPSS) low- or intermediate-1-risk myelodysplastic syndromes (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.

Methodology: 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 prerandomization 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 prerandomization 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.

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), 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.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa 40,000 IU/mL solution for injection (bulk lot numbers: BDS4300, BKS4000, CCS6100, CGS2Z00, CLS2E00, and DJS4200).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo (bulk lot numbers: BDS1J00, CCS3I00, CJS6K00, CJS7000, and DJS6V00).

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 postbaseline 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.

RESULTS:

STUDY POPULATION:

Prior to Week 24, 11 subjects in the placebo group and 15 subjects in the epoetin alfa group discontinued. Of the 34 subjects in the placebo group and the 70 subjects in the epoetin alfa group who completed through Week 24, 1 subject in the placebo group and 39 subjects in the epoetin alfa group entered the 24-week treatment 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 treatment 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.

Baseline demographics were comparable between the treatment groups. Overall, the median age was 75 years, 54.6% were men, and the median body mass index 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%). Overall, 50.0% of subjects had an Eastern Cooperative Oncology Group (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), 13.8% as refractory anemia (RA), and 13.1% as RCMD with ringed sideroblasts (RCMD-RS). For the MDS subtype according to FAB classification, the majority of all subjects (62.3%) were classified as RA and 21.5% of all subjects were classified as refractory anemia with ringed sideroblasts (RARS). Baseline mean hemoglobin values and number of RBC units per subject transfused in the 8 weeks before baseline were comparable between the groups (9.2 g/dL and 2.4 RBC units in the placebo group, 9.1 g/dL and 2.6 RBC units in the epoetin alfa group).

Major protocol deviations were noted for 53.3% of subjects in the placebo group and 62.4% of subjects in the epoetin alfa group. Most major protocol deviations were due to subjects who received an incorrect dose (35.6% in placebo group, 47.1% in epoetin alfa group) and subjects who did not meet entry criteria (22.2% and 20.0%, respectively).

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. The median weekly dose was 730.4 IU/kg in the epoetin alfa group and 850.0 IU/kg in the placebo group.

EFFICACY RESULTS:

Primary efficacy endpoint:

- 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: 31.8% (epoetin alfa group) vs. 4.4% (placebo group); p<0.001 - Fisher exact test, 2-sided. All of the responding subjects were in the strata with serum erythropoetin less than 200 mU/mL during screening.

Secondary efficacy endpoints (mITT analysis set):

- The epoetin alfa group had statistically significantly more subjects who had an erythroid response at Week 24 than the placebo group based on both the RRC evaluation (27.1% vs. 2.2%) and the investigator evaluation (36.5% vs. 4.4%), p<0.001 for both comparisons.
- Based on the ad hoc analysis 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, 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.
- Subjects in the epoetin alfa group had a mean (SD) erythroid response duration of 192.3 (88.92) days vs. 99.0 (69.30) days in the placebo group through completion of this 52-week study; however, the placebo group result is based only on 2 subjects and therefore, statistical and clinical significance should not be made.
- Eight (9.4%) subjects in the epoetin alfa group had an erythroid response at Week 24 and maintained the response through Week 48. No subjects in the placebo group completed through Week 48.
- A statistically significantly longer time (median days) to first RBC transfusion was observed in the epoetin alfa group than in the placebo group (49 days vs. 37 days, respectively; p=0.046).

  Ad hoc analyses:

  - A statistically significantly longer time (median days) to first RBC transfusion after Week 4 was observed in the epoetin alfa group than in the placebo group (142.0 days vs. 50.0 days; p=0.007).
  - A statistically significantly longer time (median days) to first RBC transfusion by RRC responder status was observed in subjects who had a response to epoetin alfa (not evaluable [NE] days) than in subjects who did not have a response to epoetin alfa (34.5 days) and all placebo subjects (37.0 days; p=0.008).
  - A statistically significantly longer time (median days) to first RBC transfusion by RRC responder status after Week 4 was observed in subjects who had a response to epoetin alfa (NE days) than in subjects who did not have a response to epoetin alfa (67.0 days) and all placebo subjects (50.0 days; p<0.001).
- 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]).
- During the first 24 weeks of the study, the percentage of subjects (calculated based on the number of active subjects) who required RBC transfusions in the epoetin alfa group steadily decreased (from 51.8% [44] of subjects in the 8 weeks prior to baseline to 24.7% [19] of subjects

between Week 16 and Week 24) and increased in the placebo group (from 48.9% [22] of subjects in the 8 weeks prior to baseline to 54.1% [20] of subjects between Week 16 and Week 24).

- For PRO/quality of life assessments (FACT-An, EQ-5D, and EQ VAS), no statistically significant difference was detected between the epoetin alfa group and the placebo group at any time point.

Ad hoc analyses based on RRC responder status (ie, IWG 2006 responders in the first 24 weeks):

- At Week 24, a statistically significant difference in improvement from baseline was observed for subjects who responded to epoetin alfa therapy compared with subjects who did not respond to epoetin alfa therapy for the total FACT An score (p=0.025), EQ-5D index score (p=0.007), and EQ VAS score (p=0.037).
- At Week 48, no statistically significant difference in improvement from baseline was observed between subjects who responded to epoetin alfa therapy and subjects who did not respond to epoetin alfa therapy for the total FACT An score (p=0.083), EQ-5D index score (p=0.075), and EQ VAS score (p=0.147).
- At Week 24, a statistically significant difference in improvement from baseline was observed for subjects who responded to epoetin alfa therapy compared with all placebo subjects for the EQ-5D index score (p=0.034); no statistically significant difference in improvement from baseline was observed between the 2 groups for the total FACT-An score (p=0.115) or EQ VAS score (p=0.282)

SAFETY RESULTS:

At Week 24, only 1 subject in the placebo group and 39 subjects in the epoetin alfa group continued in the treatment extension phase. Due to this, the primary focus of the safety analysis was based on safety data during the first 24 weeks of the study where the comparison of the 2 groups can be performed.

Summary of Key Safety Findings for the First 24 Weeks and for the Entire Study Duration

	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 acute myeloid leukemia)	4 (8.9%)	11 (12.9%)	4 (8.9%)	14 (16.5%)
Progression to acute myeloid leukemia	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.

During the first 24 weeks, the proportion of treatment-emergent adverse events was numerically higher in the placebo group as compared with the epoetin alfa group (88.9% vs. 77.6%). 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: embolism (distal deep venous thrombosis; during the first 24 weeks of treatment) and anti-erythropoietin antibody positive (after 24 weeks of treatment).

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 (ischemic stroke, embolism, and phlebitis) and one (embolism) was considered related to study agent by the investigator. Two subjects had significant risk factors (ischemic stroke [medical history of atrial fibrillation and congestive heart failure] and phlebitis [medical history of superficial thrombophlebitis]). One subject had a response to epoetin alfa at the time of the TVE (embolism). No subjects in the placebo group had a TVE.

There was a higher percentage of subjects in the placebo group with vital signs results beyond clinically important limits, at any time point during the study, than in the epoetin alfa group (51.1% vs. 41.2%, respectively).

There were no subjects with documented PRCA during the study. For 1 subject in the epoetin alfa group, anti-erythropoietin antibodies were detected (1:20, 1.0% counts per minute [cpm; a positive antibody is ≥0.9% cpm in the assay]) after Week 24.

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).

There were a total of 8 deaths during the entire study period. Five deaths were due to treatment-emergent adverse events with onset during the first 24 weeks: the 4 deaths in the epoetin alfa group were due to AML, sudden death, cachexia, and renal failure and the 1 death in the placebo group was due to AML. Three deaths were due treatment-emergent adverse events with onset after Week 24 in the epoetin alfa group: congestive heart failure, 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.

STUDY LIMITATIONS: Possible study limitations included stringent inclusion criteria at the beginning of enrollment, use of a weight-based dose along with dose modification rules based on weekly hemoglobin measurements, and use of potentially inaccurate hemoglobin values obtained from hemophotometers that were used to guide dose interruptions for some subjects; all of these contributed to the high percentage of subjects (>50%) who had major protocol deviations. An additional potential limitation was that the weekly hemoglobin measurements required per protocol led to more sensitive hemoglobin monitoring and dose interruptions than in routine clinical practice; therefore, the increase in hemoglobin and reduction in RBC transfusions required over a continuous 8-week period by the IWG 2006 erythroid response criteria were not achievable for some subjects who were clinically responding.

CONCLUSIONS:

- Treatment with epoetin alfa was effective in inducing and sustaining erythroid response, significantly reducing the percentage of subjects requiring transfusion, and prolonging the time to first RBC transfusion in subjects with IPSS low- or intermediate-1 risk MDS.
- Safety findings are consistent with the known safety profile of epoetin alfa.
- The benefit-risk profile of epoetin alfa in the treatment of anemia in subjects with IPSS low- or intermediate-1 risk MDS is positive.
- The efficacy and safety findings in this study confirm known previous clinical experience in the treatment of anemia with epoetin alfa in subjects with IPSS low- or intermediate-1 risk MDS.

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