20 July 2017
EMA/CHMP/453348/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Aranesp

International non-proprietary name: darbepoetin alfa

Procedure No. EMEA/H/C/000332/II/0142

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment Timetable

Timetable	Planned dates	Actual dates
Start of procedure:	22 April 2017	22 April 2017
CHMP Rapporteur Assessment Report	16 June 2017	19 June 2017
CHMP Co-Rapporteur Assessment Report	16 June 2017	16 June 2017
PRAC Rapporteur Assessment Report	23 June 2017	26 June 2017
PRAC members comments	28 June 2017	27 June 2017
Updated PRAC Rapporteur Assessment Report	29 June 2017	30 June 2017
PRAC Outcome	06 July 2017	06 July 2017
CHMP members comments	10 July 2017	10 July 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 July 2017	14 July 2017
Request for supplementary information	20 July 2017	20 July 2017
MAH responses	23 February 2018	Withdrawn by the Applicant on 21 February 2018

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List of abbreviations

ADR	adverse drug reaction
AML	acute myeloid leukemia
DBTP	double-blind treatment period
EOTP	end of treatment phase
EOATP	end of active treatment period
EPO	erythropoietin; ESAs
ESA	erythropoiesis-stimulating agent
FAB	French-American-British
HR	hazard ratio
IPSS	International Prognostic Scoring System
IVRS	Interactive Voice Response System
IWG	International Working Group
LTFU	long-term follow-up
MDS	myelodysplastic syndrome
Q2W	once every 2 weeks
Q3W	once every 3 weeks
RA	refractory anemia
RARS	refractory anemia with ringed sideroblasts
RBC	red blood cell
RCMD	refractory cytopenia multilineage with dysplasia in more than 1 line
rHuEPO	recombinant human erythropoietin
SC	subcutaneous
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 4 April 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include treatment of anaemia in adult patients with low transfusion demand in low or intermediate-1-risk myelodysplastic syndromes for Aranesp; as a consequence, sections 4.1, 4.2,4.8, 5.1 and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet is updated in accordance. Updated RMP version 8.0 has been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce QRD editorial changes in the SmPC, Annex IIIA and Annex IIIB.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH sought Scientific Advice from the Rapporteur BfArM three times in 2006, 2010 and 2014 and at the CHMP in 2016. Advice was given on:

BfArM 2006:

Long-term Follow-up: BfArM requested a study with 4 years of long-term follow-up to evaluate progression to AML. Amgen included a long-term follow up with a minimum of 3 years from the first dose of darbepoetin alfa.

BfArM 2010:

Placebo-controlled Treatment Period: BfArM requested that Amgen develop a phase 3 study with a 1-year placebo controlled period to better define potential adverse event risks (including AML). However, the final design of Study 20090160 included a 6-month placebo-controlled period, for 3 reasons: external experts indicated that a 1 year placebo-controlled MDS study would not be feasible due to widespread off-label use of ESAs in clinical practice; a 1 year placebo-controlled period was not considered to be ethical, as treatment guidelines (European Leukaemia Net and NCCN) recommend the use of ESAs in MDS; Amgen became aware of a large phase III 1-year-placebo-controlled study of an ESA in MDS that had terminated prematurely due to an inability to enrol subjects.

Long-term Follow-up: To evaluate long-term risk, Amgen added a long term follow up period, in which subjects are assessed with regard to survival and progression to AML every 26 weeks from the end of the treatment period through a minimum of 3 years from the first dose of investigational product.

Study Endpoints: BfArM recommended that transfusion reduction should be the primary endpoint as a measure of clinical benefit, as outlined in the Haematological Appendix of the Guideline on the Evaluation of Anticancer Medicinal Products in man.

BfArM, Nov 2014 (*italics* copied from meeting minutes; see also biometrical comments further below):

Study Endpoints: Amgen informed BfArM of the change in the primary and secondary endpoints in Amendment 3, i.e. to a primary endpoint of incidence of transfusion and secondary endpoint of IWG erythroid response. *"BfArM asked Amgen about the possible causes for the lower erythroid response rate. Amgen suggested that this was likely due to the dose adjustment rules; [….] Also these dosing rules (amongst others) may be incompatible with the IWG 2006 requirements for erythroid response"*. BfArM indicated that they would have accepted this change in endpoints at the beginning of the study, but were not supportive of this change at the end of the recruitment period and after availability of blinded scrambled data in a large number of subjects: *"BfArM challenged the scientific integrity of Protocol Amendment 3 and therefore do not support its approval. However, they did indicate that this type of protocol amendment would be acceptable for a Phase 2 non pivotal study"*. Therefore, while Protocol Amendment 3 was implemented in the other countries participating in the study, in Germany, the original protocol objectives of the study remained unchanged (ie, IWG erythroid response is the primary objective, and RBC transfusion is a secondary objective).

CHMP, Oct 2016 (*italics* copied from final advice document):

Acceptability of Study Endpoints and Study Design: Based on data provided by Amgen for Study 20090160, the CHMP indicated the acceptability of the transfusion primary endpoint and erythroid response secondary endpoint, the eligibility criteria, proposed dosing strategy, and proposed data to evaluate progression to AML. CHMP clearly pointed out that *"the dossier will ultimately be evaluated on the basis of the data presented"*, i.e., assessment will *"only depend on the overall quality of data and their analysis at the time of the type II variation"*.

2. Scientific discussion

2.1. Introduction

Myelodysplastic syndrome (MDS) is a collection of clonal stem cell disorders with common elements that include variable degrees of ineffective or hypoproliferative granulopoiesis, erythropoiesis, and megakaryopoiesis. The incidence rate of MDS is estimated to be 5.3 to 13.1 cases per 100 000 people/year worldwide and approximately 4 cases per 100 000 people/year in Europe. Patients with MDS often progress to acute myeloid leukemia (AML), particularly patients with high-risk MDS. The estimated rate of progression to AML is approximately 10% to 20% in patients with low to intermediate-1 risk MDS and 45% to 65% in patients with intermediate-2 to high risk MDS.

To harmonise MDS classifications, the French-American-British (FAB) classification was developed. With a uniform classification, MDS was better assessed with respect to its prognosis. In addition, experts developed the International Prognostic Scoring System (IPSS) based on clinical characteristics (Greenberg et al., 1997). The IPSS depends largely on the marrow blast percentage, number and extent of cytopenias, and cytogenetic abnormalities. A revised IPSS-R was developed recently (Greenberg et al., 2012); the IPSS, however, currently remains the most widely used system in clinical trials.

Patients with MDS present with variable degrees of cytopenias, with anaemia secondary to ineffective erythropoiesis being the most common presentation, affecting greater than 80% of patients with MDS. Many patients present with fatigue, dyspnea, and other symptoms related to low haemoglobin levels. As anaemia progresses, symptoms related to the low haemoglobin levels correspondingly increase.

The impact of anaemia on elderly patients, who commonly have co-existing cardiopulmonary disease, is particularly important. When compared to a control population, anaemic patients with MDS show a higher degree of fatigue and dyspnea. Anaemia at diagnosis added prognostic value to the IPSS in terms of overall survival. Specifically, patients with haemoglobin levels less than 10 g/dL had a lower life expectancy than those with haemoglobin levels greater than 10 g/dL.

While a small percentage of patients with MDS are candidates for curative therapies such as allogeneic stem cell transplantation, and a few so-called “disease modifying therapies” have been approved for the treatment of adult MDS, supportive care remains the mainstay of treatment for most MDS patients. The symptoms of anaemia may be temporarily improved by red blood cell (RBC) transfusion. In the MDS setting, increasing rates of RBC transfusions indicate disease progression according to International Working Group (IWG) 2006 response criteria definitions.

Although not approved in the EU for MDS for many years, erythropoiesis-stimulating agents (ESAs) have been used off-label to treat anaemia in patients with lower risk MDS. In early 2017, epoetin alpha (Eprex/Erypo) was the first ESA approved in the EU for treatment of symptomatic anaemia in MDS “*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)*”.

ESAs are described as first-line treatment for anaemia in patients with lower-risk MDS in the ESMO Clinical Practice Guidelines. The EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man (Appendix 4, Section 4) describes the reduction of anaemia-related symptoms as an acceptable aim of treatment in patients with MDS.

Darbepoetin alfa (in the following: darbepoetin) is a glycoengineered analogue of recombinant human erythropoietin (rHuEPO) with 2 extra consensus N-linked carbohydrate addition sites, resulting in a

longer mean residence time and a 3-fold longer serum half-life than rHuEPO. Darbepoetin stimulates erythropoiesis by the same mechanism as the endogenous hormone. Darbepoetin is approved in the EU for the treatment of symptomatic anaemia associated with chronic renal failure in adults and paediatric patients and in adult cancer patients with non-myeloid malignancies receiving chemotherapy. Darbepoetin has been approved in Turkey since 2013 for the treatment of anaemia in patients with the following subgroups of MDS: refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), and refractory cytopenia multilineage with dysplasia in more than one line (RCMD), basal erythropoietin (EPO) level ≤ 500 mU/mL before treatment, and blast count in bone marrow < 5%.

Several studies have evaluated the use of darbepoetin in anaemic patients with low to intermediate-1 risk MDS (cf. reference list module 5.4). Of these, 1 was a randomized, controlled study evaluating response rates across different doses of darbepoetin (Jang et al., 2015); the remaining studies were prospective, single-arm studies (some in combination with G-CSF). In a metaanalysis of these studies, the IWG 2000 erythroid response rate ranged from 38% to 72% (Park et al., 2016). In addition, data from a large, prospective, longitudinal, observational EU registry of MDS patients receiving ESAs off label between 2008 and 2014 for the treatment of anaemia per local guidelines showed that, amongst 539 patients for whom response to ESA treatment could be defined, responding patients had a better prognosis in terms of a lower risk of death (HR 0.65; 95% CI: 0.45, 0.893; p=0.018), whereas there was no significant effect on the risk of progression to AML (HR 0.71; 95% CI: 0.39, 1.29; p=0.27) (Garelius et al., 2016).

The current marketing application variation is intended to support the use of darbepoetin alfa for the treatment of anaemia in patients with low or intermediate-1 risk MDS with low transfusion demand. The efficacy and safety of darbepoetin alfa in this setting were evaluated in 3 studies, main phase III study 20090160 and supportive phase II study 20030207 and phase IIIb study 20130113.

2.2. Non-clinical aspects

The MAH is introducing the following new indication for Aranesp:

Treatment of anaemia in adult patients with low transfusion demand in low or intermediate-1-risk myelodysplastic syndromes (see section 5.1).

This change did not affect the non-clinical part and therefore no new clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

The applicant did not provide information on environmental risk assessment of the active ingredient darbepoetin alfa.

In compliance with the document on questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' for type II variations an ERA should be submitted if an increase in environmental exposure can be expected. In general an increase in environmental exposure is expected when the patient population is increased (e.g. the addition of a new indication). Since the applicant applies for an additional indication an increase in environmental exposure can be expected and thus an environmental risk assessment for the active ingredient darbepoetin alfa should be provided.

2.2.2. Discussion on non-clinical aspects

Since the applicant applies for an additional indication an increase in environmental exposure can be expected and thus an environmental risk assessment for the active ingredient darbepoetin alfa should be provided.

2.2.3. Conclusion on the non-clinical aspects

The following measures are considered necessary to address non-clinical issues:

Since the applicant applies for an additional indication an increase in environmental exposure can be expected and thus an environmental risk assessment for the active ingredient darbepoetin alfa should be provided.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

CHMP comment

The statement about non-EU studies in Module 1.9 refers to a wrong drug substance name. The MAH is requested to resubmit a corrected statement.

According to their CSRs, the pivotal (as well as the phase II) study were "not included in the independent Global Compliance Auditing program performed by Amgen (and PRA International, respectively)".

*The **Rapporteur requests a triggered GCP inspection** to be performed to clarify the data integrity and reliability of the results of efficacy and safety of studies 20090160 for the following reasons (section 4. Recommendations):*

Study 20090160:

- *The biometrical major objection regarding data-driven change of primary endpoint at the end of enrolment due to informative (though blinded) data review. To our understanding this data review did not take place within a SOP-controlled Blind Review or a SOP-controlled Review of the Data Monitoring Committee, therefore comprehending of the process resulting in the change of the primary endpoint is considered necessary.*
- *High number of patients excluded from the distinct primary analyses and uncertainties regarding safety evaluation (e.g. relatedness of AEs).*
- *Verification of the data regarding the incidence of RBC transfusions, the erythroid response rates and the safety information. Comparability of these aspects when different visit schedules were necessary.*

- **Tabular overview of clinical studies**

Type of Study	Protocol No.	Primary Study Objective	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	No. Subjects Enrolled	Key Entry Criteria	Duration of Study (including follow-up)	Study Status; Type of Report in MA
Reports of Efficacy and Safety Studies								
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Efficacy and Safety	20090160	To assess the superiority of darbepoetin alfa vs placebo on the incidence of red blood cell (RBC) transfusions during the 24-week double-blind treatment period in anemic subjects with low or intermediate-1 risk MDS	Phase 3, randomized, double-blind, placebo-controlled (DBTP) with open-label active treatment period (ATP)	DBTP DA 500 µg Q3W SC Placebo Q3W SC ATP DA 500 µg Q3W SC	98 DA 49 Placebo	Low and Int-1 MDS, ESA naïve, serum endogenous erythropoietin (EPO) levels ≤ 500 mU/mL at baseline Low transfusion demand (< 4 units of RBC transfusion during each of 2 consecutive 8-week periods prior to randomization)	Up to 72 weeks of treatment; minimum 3 years of follow-up	Ongoing; Full (Primary Analysis) and Supplemental (Interim Analysis)
Study Reports of Uncontrolled Clinical Studies								
Efficacy and Safety	20030207	To assess the effect of 13 weeks of darbepoetin alfa treatment on erythroid response in anemic subjects with low-risk MDS	Phase 2, stratified, single-arm, open-label	DA 500 µg Q3W SC	209 DA	Low and Int-1 MDS, ESA naive and ESA treated	Up to 52 weeks of treatment	Complete; Full (Final)
Safety	20130113	To provide access to darbepoetin alfa beyond the active treatment period of Study 20090160 and to describe the safety of longer term use	Phase 3b, single-arm, open-label companion to Study 20090160	DA at last dose received in Study 20090160	9 DA	Low and Int-1 MDS with ongoing clinically relevant erythroid response at week 70/71 in Study 20090160	Up to 73 weeks of treatment	Ongoing; Synopsis (Interim)

ATP = active treatment period; DA = darbepoetin alfa; DBTP = double blind treatment period; ESA = erythropoiesis-stimulating agent; Int-1 = intermediate-1; MA = marketing application; MDS = myelodysplastic syndrome; Q3W = once every 3 weeks; RBC = red blood cells; SC = subcutaneously.

2.3.2. Clinical pharmacology

Bioanalytical methods

Anti-darbepoetin-alpha antibody BA report (Study 20090160)

Two validated assays were used to detect the presence of anti-EPO or anti-NESP antibodies. All available protocol-specified samples were first tested in a surface plasmon resonance-based capture immunoassay to detect antibodies capable of binding to EPO or NESP (Binding Antibody Assay). Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based assay to determine neutralizing activity against EPO or NESP. If a sample was positive for binding antibodies and demonstrated neutralizing activity at the same time point, the sample was defined as positive for neutralizing antibodies.

The LLRD (lower limit of reliable detection) was 30ng/ml for anti-EPO and 60ng/ml for anti-NESP for the binding antibody assay, and 500ng/ml and 1.4µg/ml for the neutralising antibody assay, respectively.

CHMP comment

For detecting anti-darbepoetin antibodies validated assay methods were used.

As stated by the MAH, no new clinical pharmacology data are available and none were submitted. This is considered acceptable for this extension of indication.

2.4. Clinical efficacy

2.4.1. Dose response study

The proposed darbepoetin dose of 500µg Q3W proposed for the MDS setting is consistent with the approved dose in patients with chemotherapy-induced anaemia.

The efficacy and safety of this dose in subjects with MDS were initially evaluated in the **Phase II Study 20030207**.

Study title	**A Study of Darbepoetin alfa in Anaemic Subjects With Low Risk Myelodysplastic Syndrome**
Design	phase 2, stratified, multicentre, single-arm, open-label
FSI / LSLV	27 April 2004 / 05 August 2006
Sites	100 active sites in the US

Main inclusion criteria:

- Low risk MDS (low or intermediate-1 risk as defined by IPSS) and FAB classification of RA, RARS, or RAEB (with blasts ≤10%) determined by a bone biopsy and CBC within:
  - 8 weeks prior to day 1 for erythropoietin-naïve subjects, or
  - 8 weeks prior to initiation of erythropoietin treatment for currently erythropoietin-treated subjects
- Adequate iron stores determined by bone marrow film or section staining for iron by bone marrow biopsy completed within:
  - 8 weeks prior to day 1 for erythropoietin-naïve subjects, or
  - 8 weeks prior to initiation of erythropoietin treatment for currently erythropoietin-treated subjects
- ECOG performance status score of 0, 1, or 2
- Local laboratory screening haemoglobin ≤11.0 g/dL
- Adequate renal and liver function

Main exclusion criteria:

- Previous bone marrow or stem cell transplant
- History of transfusion-dependent thrombocytopenia
- Chronic myelomonocytic leukemia (CMML)
- History of PRCA
- Cardiac condition (uncontrolled angina, congestive heart failure, or uncontrolled cardiac arrhythmia)
- Uncontrolled hypertension
- Clinically significant systemic infection or chronic inflammatory disease (eg, rheumatoid arthritis)
- Serum folate ≤2.0 ng/mL or vitamin B12 ≤200 pg/mL
- Other causes of anemia (eg, hemolysis, bleeding, sickle cell anemia, renal disease)
- History of malignancies other than MDS and treated non-melanoma of the skin or in situ cervical carcinoma, within 5 years prior to screening
- Previous or ongoing use of biologic response modifiers to treat MDS, except ESA treatment, which must be discontinued at least 7 days and not more than 1 month before enrollment. The isolated use of G-CSF specifically for neutropenic fever or infection was allowed prior to study enrollment.
- Require ongoing therapy with corticosteroids other than as pre-medication for transfusions
- Any therapy used to treat MDS (including chemotherapies, antibody-based cancer treatments, hormonal therapies, interferons, and interleukins) 30 days prior to screening

- Radiotherapy within 1 year prior to screening
- Subjects planned to receive chemotherapy or radiotherapy within 28 weeks after enrollment
- Known positive antibody response to ESAs
- Known anemia treatment failure to ESAs

- ESA-naive or ESA-treated (stratification factor)
- No specifications for baseline RBC transfusion use and baseline endogenous EPO

CHMP comment

Inclusion of patients with Hb ≤11.0 g/dL at screening is higher than currently recommended for initiation of treatment for symptomatic anaemia of MDS in European treatment guidelines, i.e. ≤10.0 g/dL.

Due to no specification regarding baseline RBC transfusion status or endogenous epoetin level this could have recruited patients with high transfusion need or Epo>500mU/ml; in contrast to current recommendations as utilized in the pivotal study.

At the time of enrolment into the phase II study inclusion criteria followed the FAB classification, in the following years the MDS classifications evolved. Low risk MDS (low or intermediate-1 risk as defined by IPSS) and FAB classification of RA, RARS, or RAEB (with blasts ≤10%) determined by a bone biopsy and CBC within 8 weeks prior to day 1 for erythropoietin-naïve subjects, or …." This might have resulted in enrolment of patients with a slightly different prognostic profile in this study compared to the pivotal study.

It is emphasized that this phase II study was performed in the US only. This means that the ESA-pretreated MDS patient population intended in the proposed indication was studied in US only. The MAH should discuss whether results obtained from the studied US patient population can be extrapolated to a European MDS population.

Treatment
- 500 µg Q3W subcutaneous
- 500 µg Q2W after 6 weeks if Hb increase <1.0g/dL or to maintain Hb of 11.0-12.0g/dL;
- If Hb increased to 12.0-13.0g/dL or by >1.0g/dL in any 2-week period, the dose was to be reduced to 300 µg at the last dosing frequency.
- If Hb level reached ≥13.0 g/dL, the dose was to be withheld until Hb decreased to <12.0 g/dL, at which time darbepoetin was reinstated at 300 µg at the last dosing frequency.

CHMP comment

Overall, a fixed dose, not a weight-based dose was to be used. The initial dose of 500µg Q3W was aligned to the approved dose recommendation for chemotherapy induced anaemia.

The dose adjustment recommendations that were applicable after 6 weeks, i.e. increase of frequency to Q2W if needed, controlled the following visit scheme to be 2-weekly or 3-weekly. Also, the end of (extended) treatment period was affected (week 27 or 28; weeks 51 or 52).

Hb measures, AE reporting etc. occurred likewise at:

Q3W: weeks 4, 7, 10, 13, 16, 19, 22, 25, 28
Q2W: weeks 4, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27

And similar between weeks 31-51/52.

Due to a safety review on ESAs performed by the CHMP in 2007 the target range for titration of Hb changed from 11-12g/dl to 10-12g/dl. It is acknowledged that this study was performed when the common titration target Hb of 11-12g/dl was still higher.

Primary Objective
- To assess the effect of 13 weeks of darbepoetin alfa treatment on erythroid response in anemic subjects with low-risk MDS.

Secondary objectives
- To assess the effect of 28 weeks of darbepoetin alfa treatment on erythroid response in anemic subjects with low-risk MDS
- To assess the impact of darbepoetin alfa on hemoglobin parameters
- To assess the impact of darbepoetin alfa treatment of red blood cell (RBC) transfusion requirements
- To assess the impact of darbepoetin alfa treatment on patient-reported fatigue
- To assess the safety of darbepoetin alfa treatment in subjects with low-risk MDS

Endpoints

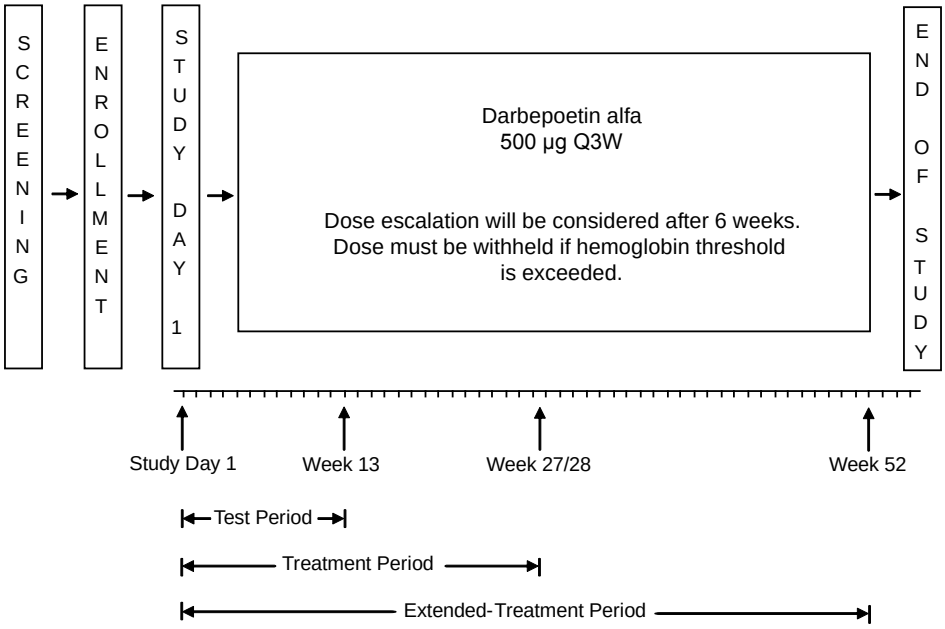
Primary: proportion of subjects achieving an erythroid response during the 13-week test period based on IWG 2000 criteria

Secondary: proportion of subjects achieving an erythroid response during the 28-week treatment period and the incidence of RBC transfusions (≥1 unit); change from baseline haemoglobin; incidence of RBC transfusions (≥1 unit); change from baseline in Functional Assessment of Cancer Therapy – Fatigue (FACT-Fatigue) scale; subject incidence of adverse events, serious adverse events, related adverse events, and severe or life-threatening adverse events; proportion of subjects with disease progression; incidence, if any, of neutralizing antibody formation to investigational product.

The efficacy analysis used 3 periods: test (weeks 1-13, primary), treatment (weeks 1-28), and extended treatment (weeks 1-52).

The test period begins on study day 1 and lasts until the end of the test period. The end of the test period is planned for the earliest of study Week 13 or 3 weeks (or 2 weeks if dose frequency is escalated) after the last dose of study drug is administered or withheld per protocol.

Figure E1 Study 20030207 Study scheme



Response / Treatment failure criteria:

Major erythroid response was defined as an increase in Hb concentration ≥2.0 g/dL above baseline in the absence of RBC transfusions during the preceding 28 days or transfusion independence (no RBC transfusions within 3 months after screening) for transfusion-dependent subjects (defined as ≥3 RBC transfusions within 3 months before screening).

Minor erythroid response was defined as an increase in Hb concentration of 1.0-2.0 g/dL above baseline in the absence of RBC transfusions during the preceding 28 days or a 50% decrease in transfusions for RBC transfusion-dependent subjects.

Treatment Failure: This is defined as an absence of erythroid response following compliant erythropoietic growth factor treatment of at least 80,000 units/week of rHuEPO for a minimum period of 6 weeks to treat anemia (Hgb <10.0 g/dL) in low-risk MDS patients.

Statistical methods

As this was a descriptive study, no formal statistical hypothesis testing was done. The analysis of efficacy and safety endpoints was performed using the primary and safety analysis sets, which included all subjects who received at least 1 dose of darbepoetin alfa. The PRO analysis set included all subjects in the primary analysis set who had completed the baseline PRO assessment and at least 1 post-baseline PRO assessment.

For the efficacy endpoints, point estimates were calculated with 95% confidence intervals. In addition, summary statistics were calculated for all endpoints. For continuous data, the mean, standard deviation, median, minimum, and maximum were provided. For discrete data, the frequency and percentage distributions were provided.

CHMP comment

To assess efficacy responses, the IWG 2000 criteria, i.e. major and minor erythroid response, were used.

The secondary efficacy endpoint after the treatment period was evaluated after 27 or 28 weeks, dependent on the ongoing dosing scheme of the patients, i.e. Q2W or Q3W.

Treatment failures were defined in CSP but none / not reported. The MAH should clarify the patients who qualified as treatment failures.

Analyses in US-only, open-label, single-arm phase II study 20030207 were descriptive only. This is considered to compromise the final B/R assessment for the ESA-pretreated patients. These are also intended in the proposed indication but were not included in the confirmatory pivotal EU phase III study.

Sample size

This study was planned to enrol approximately 200 subjects to achieve a sample size of 160 evaluable subjects for the planned analyses. Given the expected response rate for this subject population of 30%, the 95% confidence intervals were approximated to range from 18% to 42% depending on the ratio of erythropoietin-naïve subjects to erythropoietin-treated subjects enrolled in the study.

Randomisation / Blinding

Eligible subjects enrolled into the study within 7 days after screening, and the first dose of darbepoetin alfa occurred on the same day as enrollment.

This study was not blinded.

Conduct of the study

The study protocol was amended once (18 May 2004), within 2 months of the original protocol (1 March 2004). The amendment extended treatment from up to 28 weeks to up to 52 weeks and was applied to all subjects, including those subjects who enrolled under the original protocol. A summary of major changes with the amendment is provided in Table E01.

Table E01 Protocol Amendments

Amendment	Major Changes
1 (18 May 2004)	• The number of study centers was increased from 50 to 100 and the number of subjects was increased from 120 to 200 to allow increased access to the study by a geographically widespread population.
	• The inclusion criteria were modified to allow subjects currently receiving erythropoietic stimulating agent therapy possible entry into the study by stratifying the subjects as erythropoietic stimulating agent treated or naïve. In addition to expanding access to more potential subjects, this change allowed for obtaining information on subjects switching to darbepoetin alfa from erythropoietic stimulating agents with relatively shorter serum half-lives.
	• Darbepoetin alfa treatment was extended from 28 weeks to 52 weeks or to when the subject was considered treatment failure or removed from the study, whichever occurred first, to allow continued access to darbepoetin alfa after the primary and secondary endpoints were reached.

Results

Participant flow

Most of the enrolled subjects (99% erythropoietin-naïve, 98% erythropoietin-treated) were included in the primary and safety analysis sets. 75% of the subjects (79% erythropoietin-naïve, 67% erythropoietin-treated) were included in the PRO analysis sets. More than half of the enrolled subjects completed the study. A larger proportion of subjects in the ESA-pretreated stratum than in the ESA-naïve stratum discontinued the study (Table E01).

Table E02 Subject Disposition (Primary Analysis Set)

	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Subjects who were dosed	144 (100)	62 (100)	206 (100)
Subjects who completed the study	90 (63)	25 (40)	115 (56)
Subjects who did not complete the study	54 (38)	37 (60)	91 (44)
Ineligibility determined	0 (0)	1 (2)	1 (<1)
Protocol deviation	1 (1)	0 (0)	1 (<1)
Non-compliance	2 (1)	0 (0)	2 (1)
Adverse event	6 (4)	6 (10)	12 (6)
Consent withdrawn	5 (3)	9 (15)	14 (7)
Disease progression	7 (5)	1 (2)	8 (4)
Administrative decision	17 (12)	8 (13)	25 (12)
Lost to follow-up	2 (1)	0 (0)	2 (1)
Death	6 (4)	5 (8)	11 (5)
Pregnancy	0 (0)	0 (0)	0 (0)
Other	8 (6)	7 (11)	15 (7)

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Output: 14_05__t_disp.rtf (Date Generated: 15FEB07:15:27:14) Source Data: c_disp.sas7bdat
Table appears in Section 14 as Table 14-5

Demographics

A total of 206 subjects received at least 1 dose of darbepoetin and were included in the analysis. 144 subjects were ESA-naive and 62 subjects ESA treated.

Demographics were well balanced between the 2 strata. The mean age was 75.2 years. Similar proportions of subjects in both strata were either FAB classification RA (58%) or RARS (35%). The median time from MDS diagnosis to first dose was <1 month in the ESA-naive stratum and 8 months in the ESA-treated stratum.

Mean (SD) baseline Hb concentrations were 9.7 (1.0) in the ESA-naive stratum and 10.0 (1.1) g/dL in the ESA-treated stratum.

9 subjects (2 ESA-naive, 7 ESA-treated) had received ≥3 RBC transfusions in the 3 months before screening.

In study 20030207, approximately 10% of subjects had endogenous EPO levels ≥500 mU/mL.

Table E1 Baseline Disease Characteristics (Primary Analysis Set)

	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
FAB classification			
RA	81 (56)	38 (61)	119 (58)
RARS	53 (37)	20 (32)	73 (35)
RAEB	10 (7)	3 (5)	13 (6)
Missing	0 (0)	1 (2)	1 (<1)
IPSS classification			
Low	94 (65)	44 (71)	138 (67)
Intermediate-1	44 (31)	14 (23)	58 (28)
Missing	6 (4)	4 (6)	10 (5)
ECOG performance status			
0	58 (40)	27 (44)	85 (41)
1	72 (50)	28 (45)	100 (49)
2	10 (7)	3 (5)	13 (6)
3	0 (0)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)
5	0 (0)	0 (0)	0 (0)
Missing	4 (3)	4 (6)	8 (4)
Cytopenias[a]			
Hemoglobin < 10 g/dL	78 (54)	38 (61)	116 (56)
Absolute neutrophil count < 1.5 x 10^9/L	22 (15)	8 (13)	30 (15)
Platelets < 100 x 10^9/L	23 (16)	11 (18)	34 (17)
None/unknown	49 (34)	15 (24)	64 (31)
Marrow blast (%)			
< 5	124 (86)	51 (82)	175 (85)
5 to 10	11 (8)	5 (8)	16 (8)
> 10	1 (1)	0 (0)	1 (<1)
Unknown or not done	8 (6)	6 (10)	14 (7)
Cytogenetics			
Good	115 (80)	48 (77)	163 (79)
Intermediate	14 (10)	6 (10)	20 (10)
Poor	6 (4)	3 (5)	9 (4)
Unknown or not done	9 (6)	5 (8)	14 (7)

Table E2 Prior ESA Use

	Erythropoietin-Treated (N = 62) n (%)
Time (days) from start of treatment to start of study	
n	60
Mean (SD)	609.3 (637.6)
95% CL	444.6, 774.0
Median	397.5
Min, Max	23, 2592
Hemoglobin (g/dL) at start of treatment	
n	59
Mean (SD)	9.6 (1.2)
95% CL	9.3, 9.9
Median	9.6
Min, Max	5, 12
Type of erythropoietin at start of treatment - n (%)	
Darbepoetin alfa	12 (19)
Epoetin alfa	50 (81)
Type of erythropoietin at last dose - n (%)	
Darbepoetin alfa	17 (27)
Epoetin alfa	45 (73)

The majority of subjects (73%) in the ESA-treated stratum had been receiving Epoetin alfa once weekly (QW) prior to enrolment. The mean last dose of Epoetin alfa before study start was approx. 52,326 U.

Of the subjects who had received darbepoetin (27%), approximately 60% had a Q2W scheme. The mean last dose of darbepoetin before study start was approx. 232 µg.

CHMP comment

For ESA-pretreated patients mean time from ESA start to enrolment was 1.7 years. Mean Hb prior to study was 9.6g/dl.

Of the 73% patients with prior epoetin, the last QW dose was approximately 52,326 U. This corresponds to ~157,000U per 3 weeks. Calculating the darbepoetin dose from this according to current SmPC recommendations, i.e. to divide by 200, this corresponds to 785µg darbepoetin Q3W.

The 27% darbepoetin pretreated patients had a mean last dose of 232µg on a 2-weekly scheme. This corresponds to 700µg/6 weeks.

During the study, ESA-naïve patients had an average weekly darbepoetin dose of 151µg (or 2.1µg/kg/week).

ESA-pretreated patients had an average weekly darbepoetin dose of 174µg (or 2.3µg/kg/week).

Efficacy results

Primary endpoint

Table E3 Study 20030207 Erythroid response during the test period weeks 1-13

	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Erythroid response			
Major	70 (49)	16 (26)	86 (42)
95% CL for percent[a]	40, 57	15, 37	35, 48
Minor	32 (22)	11 (18)	43 (21)
95% CL for percent[a]	15, 29	8, 27	15, 26
None	42 (29)	35 (56)	77 (37)
95% CL for percent[a]	22, 37	44, 69	31, 44
Hemoglobin response			
Yes	70 (49)	16 (26)	86 (42)
No	56 (39)	33 (53)	89 (43)
Not eligible	18 (13)	13 (21)	31 (15)
Transfusion status			
Not transfusion-dependent at screening	142 (99)	55 (89)	197 (96)
Transfusion-dependent at screening[b]	2 (1)	7 (11)	9 (4)
Transfusion-independent at week 13[c]	0 (0)	0 (0)	0 (0)
≥ 50% decrease in transfusions at week 13[d]	1 (1)	1 (2)	2 (1)
< 50% decrease in transfusions (or status indeterminable) at week 13	1 (1)	6 (10)	7 (3)

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[a] Binomial proportion with CLs calculated by using the normal approximation.
[b] Transfusion-dependent subjects are defined as those who received ≥ 3 RBC transfusions in the 13 weeks (3 months) before screening.
[c] Transfusion-independent subjects are defined as those who remained in the study through week 13 and had no RBC transfusions in that time.
[d] A ≥ 50% decrease in transfusions is calculated based on a comparison of the number of transfusions before screening and the number of transfusions from weeks 1 to 13.

CHMP comment

The primary endpoint of erythroid response after 13 weeks test period was reached in ESA-treated and ESA-naïve patients. 49% naïve had a major, 22% naïve a minor response. In ESA-pretreated responses were observed at 26% and 18%, respectively.

13 and 21% were counted as not-eligible for the 1°EP haemoglobin response.

For responses counted as transfusion reduction in ESA-treated patients only 1 of 7 had a >50% reduction in transfusions.

It has to be noted that these results were observed under dose-adjustment possibilities.

Secondary endpoints

During the treatment period (weeks 1-27/28), the proportions of subjects who achieved a major erythroid response were 58% and 31% in the ESA-naive and ESA-treated strata, respectively.

During the extended treatment period (weeks 1-51/52), the proportions of subjects who achieved a major erythroid response were 59% and 34% in the ESA-naive and ESA-treated strata, respectively.

Similar to the results observed for the primary endpoint, subjects with RA or RARS within the ESA-naïve stratum had a larger proportion of subjects with erythroid responses than the other subgroups (ESA-naïve RAEB and all MDS subtypes within the ESA-treated stratum).

Table E4 Erythroid response during the test period by FAB classification

FAB Classification: RA

	Erythropoietin-Naïve (N = 81) n (%)	Erythropoietin-Treated (N = 38) n (%)	All Subjects (N = 119) n (%)
Erythroid response			
Major	45 (56)	14 (37)	59 (50)
95% CL for percent[a]	(45, 66)	(22, 52)	(41, 59)
Minor	14 (17)	7 (18)	21 (18)
95% CL for percent[a]	(9, 26)	(6, 31)	(11, 24)
None	22 (27)	17 (45)	39 (33)
95% CL for percent[a]	(17, 37)	(29, 61)	(24, 41)
Hemoglobin response			
Yes	45 (56)	14 (37)	59 (50)
No	30 (37)	17 (45)	47 (39)
Not eligible	6 (7)	7 (18)	13 (11)
Transfusion status			
Not transfusion-dependent at screening	80 (99)	34 (89)	114 (96)
Transfusion-dependent at screening[b]	1 (1)	4 (11)	5 (4)
Transfusion-independent at week 13[c]	0 (0)	0 (0)	0 (0)
≥ 50% decrease in transfusions at week 13[d]	0 (0)	1 (3)	1 (1)
< 50% decrease in transfusions (or status indeterminable) at week 13	1 (1)	3 (8)	4 (3)

FAB Classification: RARS

	Erythropoietin-Naïve (N = 53) n (%)	Erythropoietin-Treated (N = 20) n (%)	All Subjects (N = 73) n (%)
Erythroid response			
Major	23 (43)	1 (5)	24 (33)
95% CL for percent[a]	(30, 57)	(0, 15)	(22, 44)
Minor	15 (28)	4 (20)	19 (26)
95% CL for percent[a]	(16, 40)	(2, 38)	(16, 36)
None	15 (28)	15 (75)	30 (41)
95% CL for percent[a]	(16, 40)	(56, 94)	(30, 52)
Hemoglobin response			
Yes	23 (43)	1 (5)	24 (33)
No	22 (42)	14 (70)	36 (49)
Not eligible	8 (15)	5 (25)	13 (18)
Transfusion status			
Not transfusion-dependent at screening	52 (98)	18 (90)	70 (96)
Transfusion-dependent at screening[b]	1 (2)	2 (10)	3 (4)
Transfusion-independent at week 13[c]	0 (0)	0 (0)	0 (0)
≥ 50% decrease in transfusions at week 13[d]	1 (2)	0 (0)	1 (1)
< 50% decrease in transfusions (or status indeterminable) at week 13	0 (0)	2 (10)	2 (3)

FAB Classification: RAEB

	Erythropoietin-Naïve (N = 10) n (%)	Erythropoietin-Treated (N = 3) n (%)	All Subjects (N = 13) n (%)
Erythroid response			
Major	2 (20)	1 (33)	3 (23)
95% CL for percent[a]	(0, 45)	(0, 87)	(0, 46)
Minor	3 (30)	0 (0)	3 (23)
95% CL for percent[a]	(2, 58)	(0, 0)	(0, 46)
None	5 (50)	2 (67)	7 (54)
95% CL for percent[a]	(19, 81)	(13, 100)	(27, 81)
Hemoglobin response			
Yes	2 (20)	1 (33)	3 (23)
No	4 (40)	1 (33)	5 (38)
Not eligible	4 (40)	1 (33)	5 (38)
Transfusion status			
Not transfusion-dependent at screening	10 (100)	2 (67)	12 (92)
Transfusion-dependent at screening[b]	0 (0)	1 (33)	1 (8)
Transfusion-independent at week 13[c]	0 (0)	0 (0)	0 (0)
≥ 50% decrease in transfusions at week 13[d]	0 (0)	0 (0)	0 (0)
< 50% decrease in transfusions (or status indeterminable) at week 13	0 (0)	1 (33)	1 (8)

CHMP comment

While for ESA-naïve patients FAB classes RA and RARS showed comparable erythroid responses of overall >80%, the ESA-pretreated patients had more responses (55%) in the RA compared to 25% in the RARS class. This result is expectable as RA patients are known to better respond to ESAs than RARS patients.

Results in RAEB class were better in naïve patients, but numbers were too small to draw valid conclusions.

RBC transfusions during the test period, treatment period, and extended treatment period are provided in Table E5. Across all periods evaluated, the incidence of RBC transfusions was lower in the ESA-naive stratum than in the ESA-treated stratum. During the extended treatment period the mean (SD) number of units transfused were 2.4 (6.7) and 4.6 (9.1) units in the ESA-naïve and ESA-treated strata, respectively.

Table E5 RBC transfusions

	ESA-naive (N = 144) n (%)	ESA-treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Test Period (Weeks 1 to 13)			
Subjects with RBC transfusion	24	20	44
Kaplan-Meier Percent (95% CL)[a]	17 (11, 23)	35 (22, 47)	22 (16, 28)
Crude percent (95% CL)[b]	17 (11, 23)	32 (21, 44)	21 (16, 27)
Treatment Period (Weeks 1 to 28)			
Subjects with RBC transfusion	26	21	47
Kaplan-Meier Percent (95% CL)[a]	18 (12, 25)	37 (24, 50)	24 (18, 30)
Crude percent (95% CL)[b]	18 (12, 24)	34 (22, 46)	23 (17, 29)
Extended Treatment Period (Weeks 1 to 52)			
Subjects with RBC transfusion	37	23	60
Kaplan-Meier Percent (95% CL)[a]	28 (20, 36)	42 (29, 56)	32 (25, 39)
Crude percent (95% CL)[b]	26 (19, 33)	37 (25, 49)	29 (23, 35)

Mean (SD) baseline Hb concentrations were 9.7 (1.0) and 10.0 (1.1) g/dL for the ESA-naïve and ESA-treated strata, respectively. Mean changes from baseline in Hb concentrations (using the LVCF approach) ranged from 1.1-1.4 g/dL in the ESA-naïve stratum and from 0.3-0.5 g/dL in the ESA-treated stratum (Table E6). In general, mean increases from baseline were larger in the ESA-naïve stratum than the ESA-treated stratum.

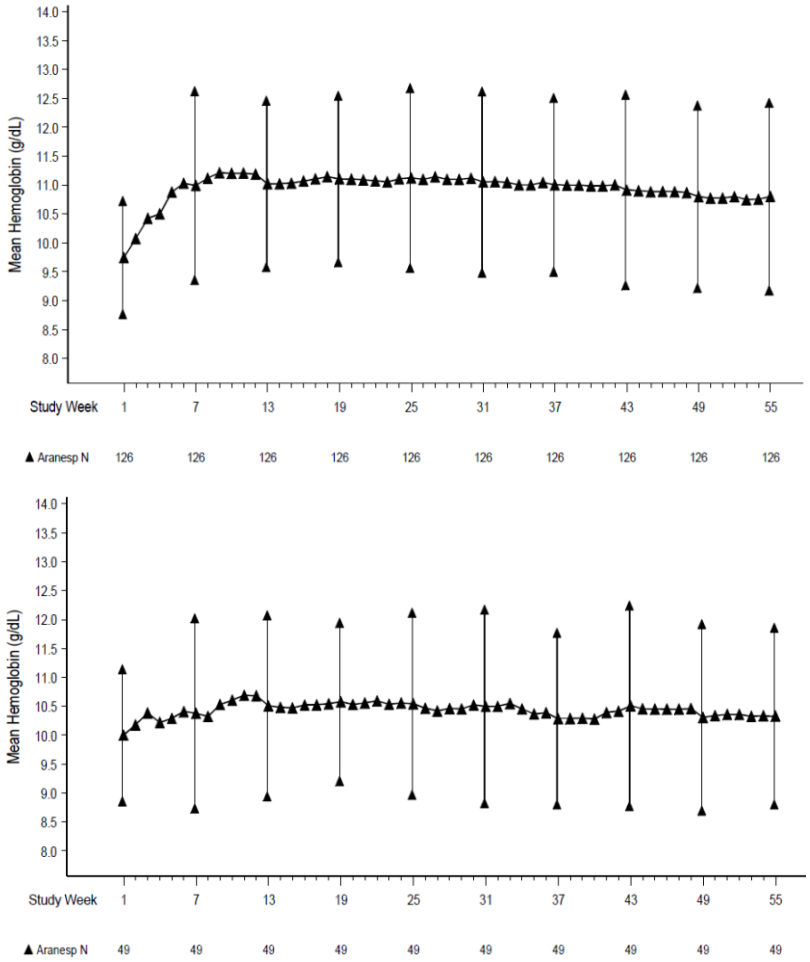
Subjects with RARS in the ESA-treated stratum had mean decreases of Hb from baseline of 0.2-0.3 g/dL.

Table E6 Change in haemoglobin concentration

	LVCF Approach		
	Erythropoietin-Naïve (N = 126)	Erythropoietin-Treated (N = 49)	All Subjects (N = 175)
Hemoglobin at week 1 (baseline)			
n	126	49	175
Mean (SD)	9.7 (1.0)	10.0 (1.1)	9.8 (1.0)
95% CL	9.6, 9.9	9.7, 10.3	9.7, 10.0
Median	9.9	10.2	9.9
Min, Max	6.9, 11.6	6.7, 13.9	6.7, 13.9
Change in hemoglobin from baseline to week 13			
n	126	49	175
Mean (SD)	1.3 (1.2)	0.5 (1.4)	1.1 (1.3)
95% CL	1.1, 1.5	0.1, 0.9	0.9, 1.3
Median	1.2	0.2	1.0
Min, Max	-1.9, 5.2	-2.6, 4.1	-2.6, 5.2
Change in hemoglobin from baseline to week 27/28			
n	126	49	175
Mean (SD)	1.4 (1.4)	0.5 (1.7)	1.1 (1.5)
95% CL	1.1, 1.6	-0.0, 1.0	0.9, 1.4
Median	1.4	0.3	1.1
Min, Max	-1.9, 5.0	-3.1, 4.5	-3.1, 5.0
Change in hemoglobin from baseline to week 37			
n	126	49	175
Mean (SD)	1.3 (1.4)	0.3 (1.5)	1.0 (1.5)
95% CL	1.0, 1.5	-0.1, 0.7	0.8, 1.2
Median	1.3	0.1	1.1
Min, Max	-1.9, 4.7	-3.7, 2.8	-3.7, 4.7
Change in hemoglobin from baseline to week 53/55			
n	126	49	175
Mean (SD)	1.1 (1.5)	0.3 (1.7)	0.9 (1.6)
95% CL	0.8, 1.3	-0.2, 0.8	0.6, 1.1
Median	1.0	0.3	0.8
Min, Max	-2.0, 4.8	-3.7, 3.2	-3.7, 4.8

The target haemoglobin assessment was the proportion of subjects with baseline haemoglobin concentrations <11 g/dL who achieved the target haemoglobin concentration (≥11 g/dL).
92 (of 129 eligible) erythropoietin-naïve and 26 (of 57) erythropoietin-treated subjects achieved the target haemoglobin concentration. (Kaplan-Meier estimates were 82% and 55%, respectfully; Figure E2). The median times to achieving the target haemoglobin concentration were 7.0 and 24.0 weeks in the ESA-naïve and ESA-treated strata, resp.

Figure E2 Mean (SD) Hb concentrations (ESA-naïve [upper], ESA-treated [lower])



CHMP comment

Overall the ESA-pretreated patients did not respond as well as the ESA treatment-naïve patients over the complete treatment period for Hb response.

As derived from the exposure data (safety section), of the ESA-treated patients 15% (vs. 4% naïve) did not receive >4 weeks of treatment, which is comparable to 15% (vs. 3%) who withdrew consent. This could be seen as stopping the study early due to underdosing.

From figure E2 it seems that especially in the ESA-treated stratum dose increases after 6 weeks were performed in order to obtain the target Hb of >11g/dl. In view of the fact that the darbepoetin-pretreated patients had mostly been on a Q2W scheme with a mean of 232 µg/dose (= approx. 700µg/6 weeks) but still had a Hb of <10g/dl, the starting Q3W dosing of 500µg (=1000µg/6 weeks) seems to have not been sufficiently effective; similarly for epoetin-treated patients in comparison to the pre-study dose.

For comparison, in the pivotal study of epoetin alpha in naïve and pretreated patients, where dose increases were allowed, the weekly mean average dose was 683.1 IU/kg.

The MAH should discuss possible differences in (early) responses between epoetin and darbepoetin-pretreated patients and whether the proposed fixed (starting)-dose recommendation of 500µg Q3W has similar benefit in both groups, especially when switching the ESA.

In contrast, the MDS patients in the ESA-naïve stratum showed a steep Hb increase during the first 6 weeks with the 500µg Q3W scheme up to the target Hb concentration of >11g/dl.

*In the CSR of study 20030207 the MAH discussed "*An evaluation of haemoglobin response by dosing schedule indicated that increasing the dosing frequency from Q3W to Q2W resulted in little benefit. Among subjects in the erythropoietin-naïve stratum who achieved a haemoglobin response during the entire study, most subjects (82%) achieved that response without a dose increase*."*

No information could, however, be found in the dossier/CSR about necessary dose increases or decreases according to protocol after week 6. The MAH is asked to provide information about the changes from Q3W to Q2W in both strata during the extended treatment period, including the referenced evaluation of response by dosing scheme.

Treatment failures were defined in CSP but none / not reported.

Due to the primary efficacy result in the ESA-naïve stratum, as well as the safety results, the MAH decided upon a recommended phase III dose of 500µg Q3W in patients with low-risk and intermediate-1 MDS.

Patient-reported outcomes

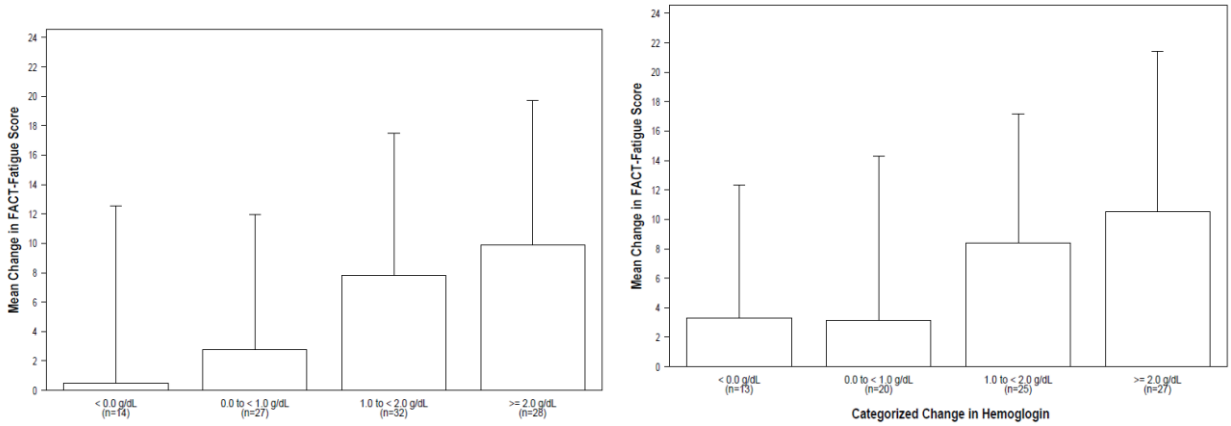
Mean (SD) baseline FACT-Fatigue scores were 30.1 (13.5) and 31.1 (11.5) in the ESA-naïve and ESA-treated strata, respectively. Mean changes from baseline in FACT-F scores during the extended treatment period ranged from 5.6 to 6.8 for the ESA-naïve stratum and from -2.1 to 6.2 in the ESA-treated stratum. In general, subjects with RA or RARS had larger and more consistent increases from baseline in mean FACT-F scores than subjects with RAEB. In both strata, larger mean increases from baseline in FACT-F scores were observed for subjects with increases from baseline in Hb of 2.0 g/dL (6.3 to 10.5) compared with subjects with changes from baseline in Hb of <1.0 g/dL (-8.3 to 3.3).

Table E7 Change in FACT-Fatigue score during the extended treatment period

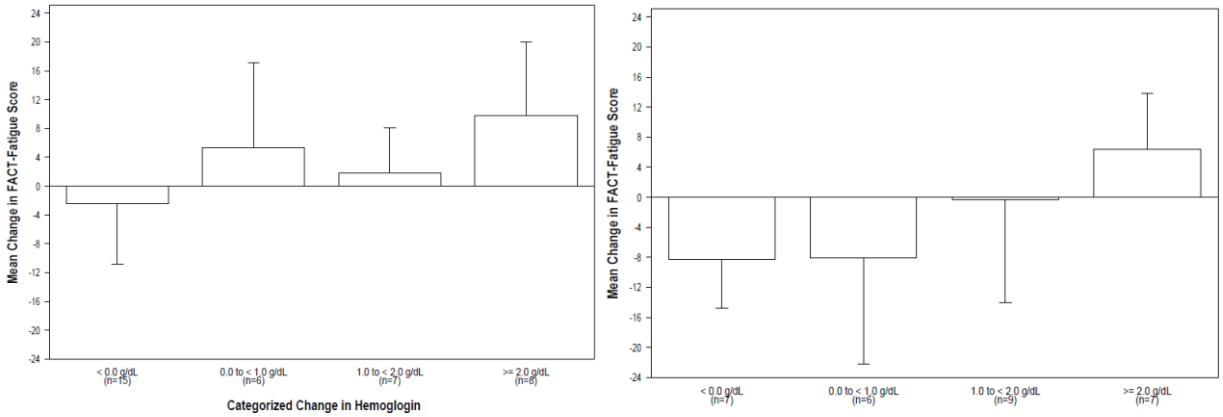
	Erythropoietin-Naïve (N = 115)	Erythropoietin-Treated (N = 42)	All Subjects (N = 157)
FACT-F score at week 1 (baseline)			
n	115	42	157
Mean (SD)	30.1 (13.5)	31.1 (11.5)	30.4 (12.9)
95% CL	27.7, 32.6	27.6, 34.7	28.4, 32.4
Median	31.0	31.0	31.0
Min, Max	3.0, 52.0	12.0, 52.0	3.0, 52.0
Change in FACT-F score from baseline to week 13			
n	104	36	140
Mean (SD)	5.6 (10.7)	2.4 (10.0)	4.8 (10.6)
95% CL	3.5, 7.7	-0.9, 5.8	3.0, 6.6
Median	4.0	0.0	3.0
Min, Max	-27.0, 30.0	-18.0, 26.0	-27.0, 30.0
Change in FACT-F score from baseline to week 25			
n	93	30	123
Mean (SD)	6.8 (10.6)	-2.1 (11.9)	4.6 (11.5)
95% CL	4.6, 9.0	-6.6, 2.3	2.6, 6.7
Median	4.0	-0.6	2.6
Min, Max	-12.0, 32.0	-30.0, 23.0	-30.0, 32.0
Change in FACT-F score from baseline to week 37			
n	83	27	110
Mean (SD)	6.7 (10.6)	3.8 (10.5)	6.0 (10.6)
95% CL	4.4, 9.0	-0.4, 8.0	4.0, 8.0
Median	4.1	4.0	4.0
Min, Max	-20.0, 35.0	-18.0, 20.0	-20.0, 35.0
Change in FACT-F score from baseline to week 53/55			
n	70	17	87
Mean (SD)	6.2 (9.4)	6.2 (8.8)	6.2 (9.2)
95% CL	4.0, 8.4	1.7, 10.7	4.2, 8.2
Median	5.0	8.0	5.0
Min, Max	-12.3, 32.0	-11.0, 23.0	-12.3, 32.0

Figure E3 Change in FACT-Fatigue Scores from Baseline to week 13 (left) and week 25 (right)

a) ESA-naïve



b) ESA-pretreated



Mean changes in other PRO assessments, including the EQ-5D and Energy and overall health assessment (EOHA), did not demonstrate any trends over time.

CHMP comment

Of the 3 tested HRQOL questionnaires (including EQ-5D and EOHA) only the FACT-F(atigue) showed trends over time. Fatigue is one of the major symptoms of anaemia which impairs QoL in MDS patients and is considered relevant for treatment benefit.

For the ESA-naïve patients clinically relevant changes, i.e. 3 and higher, were seen from the test period week 13 and ongoing and only in the Hb responder groups. For the ESA-treated patients a stable clinically relevant increase was only visible in the patients with a major Hb response. In this regard it has to be noted that the positive score changes in the ESA-treated group were only observed when the numbers of completed questionnaires decreased, i.e. non-responders had left the treatment and/or study.

Subjects with RA or RARS had larger and more consistent increases from baseline in mean FACT-F scores than those with RAEB, however, patients numbers for the RAEB group are too small (2-6) to draw valid conclusions.

In general, standard deviations were high so that no further conclusions can be drawn.

2.4.2. Main study

A Multicenter, Randomised, Double-blind, Placebo-controlled Study of Darbepoetin alfa for the Treatment of Anaemic Subjects With Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Study Code	20090160
EudraCT	2009-016522-14
Design	phase 3, randomised, double-blind, multicentre
FSI / LSLV	21 December 2011 / N/A, study is ongoing
Data cut-off	07 October 2015
Sites	49 active sites in the EU

In addition to the CSR for the primary analysis, a second CSR for an interim analysis of the data until the end of the active treatment period was submitted:

Data cut-off	18 February 2016

Methods

Study participants

Inclusion criteria

- Low or intermediate-1 risk MDS patients per IPSS at the time of randomisation, as determined by complete blood count (CBC) during screening and bone marrow examination and marrow cytogenetic analysis performed within 16 weeks prior to randomisation. Subject cannot have been rendered low or intermediate-1 risk by prior disease modifying therapy.
- WHO classification of refractory anaemia (RA), refractory anaemia with ring sideroblasts (RARS), refractory cytopenias with multilineage dysplasia (RCMD), MDS-unclassified (MDS-U), MDS with isolated del(5q) (5q- syndrome) or refractory anaemia with excess blasts-1 (RAEB-1)
- ECOG performance score 0 or 1
- Haemoglobin level ≤ 10.0 g/dL within 7 days prior to randomisation
- Transferrin saturation (Tsat) ≥ 15% and serum ferritin ≥ 10 ng/mL
- Serum folate ≥ 4.5 nmol/L [≥ 2.0 ng/mL] or RBC folate ≥ 317 nmol/L [≥ 140 ng/mL]
- Vitamin B12 ≥ 148 pmol/L [≥ 200 pg/mL]
- ≥18 years of age
- Subject or subject's legally acceptable representative has provided informed consent

Exclusion Criteria

- Previously diagnosed with intermediate-2 or high risk MDS per IPSS
- Therapy-related or secondary MDS
- History of acute leukemia
- Evidence of bone marrow collagen fibrosis
- Inherited anaemia (eg, haemoglobinopathy, thalassemia, red cell membrane defect, red cell enzyme deficiency), active hemorrhage, red cell aplasia, haemolytic anaemia
- History of malignancies other than curatively treated non-melanoma skin or in situ carcinoma
- History of thrombosis within 6 months

- Previous bone marrow or stem cell transplantation
- Uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia, known myocardial infarction within 6 months
- Uncontrolled hypertension defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg
- Clinically significant systemic infection or uncontrolled chronic inflammatory disease (ie, rheumatoid arthritis, inflammatory bowel disease)
- History of seizure disorder
- Previous or ongoing use of ESA therapy, eg., rHuEpo, darbepoetin alfa
- High transfusion demand: ≥ 4 units of RBC transfusion during either of 2 consecutive 8-week periods (ie, days -113 to -57 or days -56 to 0) prior to randomisation
- Received any RBC transfusion within 14 days prior to randomisation
- Received cytotoxic chemotherapy for any oncologic indication or planned during the double-blind treatment period
- Received biologic response modifiers (eg, thalidomide, lenalidomide, arsenic trioxide, azacitidine, decitabine) to treat MDS or planned during the double-blind treatment period
- Received myeloablative or craniospinal radiation or planned during the double-blind treatment period
- Received G-CSF therapy within 30 days prior to randomisation or planned during the double-blind treatment period (temporary use of G-CSF for neutropenia with fever and/or infection is acceptable)
- Abnormal renal function (serum creatinine level > 2 x ULN)
- Abnormal liver function (total bilirubin > 2 x, ALT AST > 3 x ULN)
- Serum endogenous EPO level >500 mU/mL
- Known HIV or AIDS, positive hepatitis B surface antigen or hepatitis C
- Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)
- Females is not willing to use highly effective contraception during treatment and for at least 1 month after the end of treatment
- Females is pregnant or planning to become pregnant within 1 month after the end of treatment
- Confirmed history of neutralising antibody activity to rHuEpo or darbepoetin alfa

CHMP comment

The pivotal study enrolled Low-or Int-1 primary MDS patients with RA, RARS, RCMD; MDS-U, del5q, or RAEB-1 according to WHO 2008 classification. Hb-level had to be ≤10g/dl at baseline with adequate transferrin and ferritin saturation.

Secondary MDS, Int-2 or high-risk MDS and a history of AML were excluded. Patients must not have had high transfusion demand (≥4 units of RBC transfusions within 8 weeks) or received transfusion during the 14 days prior to randomisation. Endogenous EPO levels had to be <500mU/ml. Pretreatment with ESAs, disease modifiers or cytotoxic chemotherapy was also excluded.

In general, the in- and exclusion criteria of the pivotal study defined an ESA-naïve MDS population which corresponds to the current European guideline recommendations for initiating ESA therapy.

Treatments

Investigational product was provided in single dose vials of human serum albumin (HSA)-free polysorbate solution that is a clear, colourless, sterile, preservative-free protein solution. Each vial contained 500 µg, 300 µg, 200 µg, or 100 µg of darbepoetin per mL or placebo (without the active drug).

Placebo was presented in identical containers and stored/packaged the same as darbepoetin.

Dose adjustments were based on the most recent local laboratory haemoglobin value (obtained on the day of the dosing visit or 1 day prior to the dosing visit) and RBC transfusion information, and were controlled by an IVRS throughout the study.

During the double blind treatment period (DBTP), subjects received 500 µg darbepoetin SC or matched placebo once every 3 weeks (Q3W) from day 1/week 1 to week 22. Dose escalation was not permitted during the DBTP, only at or after week 31.

At or after week 31, for subjects with a haemoglobin increase of <1.5 g/dL (relative to week 1 for darbepoetin subjects and relative to week 25 for placebo subjects) and in the absence of RBC transfusion in the prior 28 days, the dose was escalated (eg, from 500 µg Q3W to 500 µg Q2W).

If the dose was adjusted to Q2W, the Q2W dose frequency was then maintained for the duration of the active treatment period, even if the dose was later reduced.

Dose reduction was permitted at any time for the following reasons:

- Exceeding haemoglobin threshold: If haemoglobin reached >12.0 g/dL, the IVRS instructed the investigator to temporarily withhold IP until haemoglobin falls to ≤11.0 g/dL at which time treatment will be restarted at a reduced dose (ie, 500 µg to 300 µg; 300 µg to 200 µg; 200 µg to 100 µg) (maintain previous dosing frequency of Q3W or Q2W).
- Excessive rate of rise: If haemoglobin increased by > 1.5 g/dL in any 21-day period for Q3W dosing or > 1.0 g/dL in any 14-day period for Q2W dosing in the absence of RBC transfusion, the dose was reduced from the previous dose (ie, 500 µg to 300 µg; 300 µg to 200 µg; 200 µg to 100 µg) (maintain previous dosing frequency of Q3W or Q2W).

A maximum of 3 dose reductions were permitted during the study. Should a subject meet the criteria for a fourth dose reduction, the subject was to be discontinued from IP. Subjects should then enter the LTFU period.

Table E8 Dose at Week 25 in the active treatment period based on last dose DBTP

Last Dose Assigned at Week 22 in the Double-blind Treatment Period	Dose Assigned at Week 25 in the Active Treatment Period
500 µg Q3W	500 µg Q3W
300 µg Q3W	300 µg Q3W
200 µg Q3W	200 µg Q3W
100 µg Q3W	100 µg Q3W
Placebo	500 µg Q3W
IP withheld; previous dose was 500 µg Q3W	Reinstated at 300 µg Q3W (if Hb ≤ 11 g/dL)
IP withheld; previous dose was 300 µg Q3W	Reinstated at 200 µg Q3W (if Hb ≤ 11 g/dL)
IP withheld; previous dose was 200 µg Q3W	Reinstated at 100 µg Q3W (if Hb ≤ 11 g/dL)
IP discontinued (eg, if 3 previous dose reductions were required)	Darbepoetin alfa not assigned

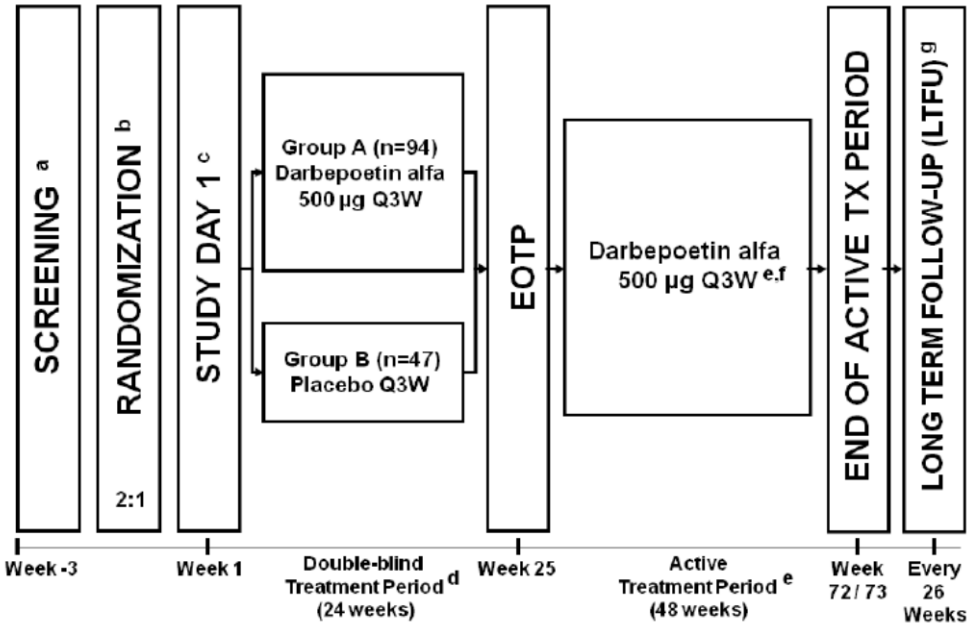
CHMP comment

Dose adjustments in the pivotal study were operated by the IVRS system based on local lab Hb.

Dose increase and reduction requirements of the pivotal study are comparably reflected in proposed SmPC section 4.2. However, the dose increase recommendations were not subject of the blinded randomised treatment phase of the phase III study and hence not confirmed with the primary endpoint. The MAH is requested to discuss the justifiability of the proposed dose increase recommendations.

The proposed wording in section 4.2 is, in addition, necessary to adjust to reflect a "common SmPC recommendation phrasing", as currently it reflects the obligatory wording of a study protocol "dose is escalated" or "reduction is permitted".

Figure E4 Study design and treatment scheme



a. The screening period, which starts when the subject signs and dates the informed consent and ends when the subject is randomised, must not exceed 21 days.

b. Eligible subjects are randomised 2:1 (darbepoetin alfa:placebo), stratified by the International Prognostic Scoring System (IPSS) category (low versus intermediate-1) established at screening.

c. The first dose of double-blind IP (ie, study day 1) may be administered on the day of randomisation or up to 4 days after randomisation (ie, randomisation may occur on days -3, -2, -1, 0, or 1).

d. During the double-blind treatment period, subjects receive double-blind darbepoetin alfa Q3W subcutaneous (SC) or matched placebo Q3W SC from day 1 / week 1 to week 22. Dosing is initiated at darbepoetin alfa 500 µg.

e. Entering the active treatment period at week 25, all subjects receive darbepoetin alfa 500 µg Q3W SC, or, for those subjects who were receiving darbepoetin alfa during the double-blind treatment period and were dose-reduced, the last dose assigned during the double-blind treatment period. During the active treatment period, subjects receive darbepoetin alfa Q3W SC from week 25 to week 31 and darbepoetin alfa Q3W or Q2W SC from week 31 to week 70 / 71.

f. At or after week 31, for subjects with a haemoglobin increase of < 1.5 g/dL (relative to week 1 for darbepoetin alfa subjects and relative to week 25 for placebo subjects) and in the absence of RBC transfusion in the prior 28 days, the dose will be escalated (eg, from 500 µg Q3W to 500 µg Q2W).

g. Long-term follow-up (LTFU) will occur every 26 weeks (± 4 weeks) from the EOATP visit (or EOTP visit if the subject does not enter the active treatment period) and will continue for a minimum of 3 years from the first dose of IP. Follow-up may occur through clinic visit or telephone contacts. Survival and progression to AML status will be collected during LTFU. Example outlines for LTFU can be found in Appendix L.

CHMP comment

It is noted from the study protocol that during the active treatment period after week 31 the visits and herewith the visits' study procedures were performed every 2 weeks for patients on Q2W dosing scheme compared to maintenance of every 3 weeks for patients on Q3W scheme: "Study visits through week 31 will occur every 3 weeks ± 6 days with darbepoetin alfa administration Q3W SC. After the week 31 study visit, the subsequent visit schedule is determined by the darbepoetin alfa dosing frequency (ie, Q3W or Q2W) and at which study visit a subject is switched from Q3W to Q2W dosing (if appropriate). At or after week 31, if the darbepoetin alfa dosing frequency is switched from Q3W to Q2W, study visits will occur every 2 weeks ± 6 days with darbepoetin alfa administration Q2W SC for the duration of the active treatment period*". Especially for collection of adverse events and Hb this is considered as certainly have introduced bias.*

Objectives

General Remark
The applicable protocol in Germany is version 2.0, dated 25th of September 2013.
The applicable protocol in countries except Germany is version 4.0, dated 10th of august, 2015.
Both protocols are on an equal footing.

Primary Objective

For countries except Germany:
To assess the superiority of darbepoetin alfa vs placebo on the incidence of RBC transfusions during the 24-week double-blind treatment period in anaemic subjects with low or intermediate-1 risk MDS.

For Germany:
To assess the superiority of darbepoetin alfa treatment compared with placebo treatment on the proportion of subjects achieving International Working Group (IWG) erythroid response (Cheson et al, 2006) during the 24-week double-blind treatment period in anaemic subjects with low or intermediate-1 risk MDS. IWG erythroid response for non-transfusion dependent subjects is defined as a haemoglobin level increase of ≥ 1.5 g/dL compared with the baseline haemoglobin level and sustained over 8 weeks in the absence of red blood cell (RBC) transfusion.

Biometrical comment

ICH-GCP (E6) defines: "1.40 multicentre Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator." Since a multicentre study includes also multinational studies, this requirement does also hold for multinational studies. The study 20090160 is not in line with ICH-GCP (E6) requirements.

Secondary Objectives

- To assess the superiority of darbepoetin alfa treatment compared with placebo treatment on the proportion of subjects achieving IWG erythroid response (Cheson et al, 2006) during the 24-week double-blind treatment period in anaemic subjects with low or intermediate-1 risk MDS.
- To assess the safety of darbepoetin alfa compared with placebo
- To assess the health-related quality of life (HRQOL) scores of darbepoetin alfa compared with placebo, and to assess the effect of haemoglobin change on HRQOL scores

Protocol Amendment 3, which changed the primary objective to RBC transfusion and the secondary objective to IWG erythroid response, was not implemented in Germany. Therefore, in Germany, the original protocol objectives of the study remain unchanged (i.e., RBC transfusion is a secondary objective).

Outcomes / endpoints

Primary Endpoint

General Remark
The applicable protocol in Germany is version 2.0, dated 25th of September 2013. The applicable protocol in countries except Germany is version 4.0, dated 10th of august, 2015. Both protocols are equally effective. Both versions do define a different primary endpoint.

Other Countries except Germany (Protocol 4.0, p. 62):
The proportion of subjects with at least 1 RBC transfusion from week 5 to EOTP will be analysed using a Chi-squared test for differences and using the CMH method stratified by the IPSS category (low versus intermediate-1). The analysis will be performed on subjects in the Transfusions from Week 5 to EOTP Primary Analysis Set.

Germany (Protocol 2.0, p. 58)
Achieving an IWG erythroid response during the double-blind treatment period.
IWG erythroid response for non-transfusion dependent subjects is defined as achieving an initial ≥ 1.5 g/dL increase from baseline in haemoglobin level and sustaining an average rise of ≥ 1.5 g/dL in a rolling 56-consecutive day period in the absence RBC transfusion.
IWG erythroid response will be determined based on central laboratory haemoglobin values.

Biometrical comment

ICH-GCP (E6) defines: "1.40 multicentre Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator." Since a multicentre study includes also multinational studies, this requirement does also hold for multinational studies. The study 20090160 is not in line with ICH-GCP (E6) requirements, and also in that respect not in line with ICH E9 requirements.

The problem of having no unique and clear criterion for deciding when the trial is successful, is fully evident when the situation of having two effective primary endpoint related to different versions of the protocol.

First, the national scientific advice meeting (Germany, 20 November 2014) will be reflected. Then the assessment makes use of two relevant guidelines – Reflection paper on methodological issues in confirmatory issues in confirmatory and clinical trials with adaptive design – *and* -ICH E9 Statistical Principles for Clinical Trials*.*

Although, the study of interest has not an adaptive design, the guidance is considered relevant. The sponsor did not use a predefined interim analysis. The growing database of incoming data of the study was used not within a framework of an interim analysis, but to program the tables and figures etc., that would be needed for the primary analysis. The review of the data was therefore not a planned interim analysis. The programmer of the tables realized that the primary endpoint data where not as expected and that it would be unlikely that the primary endpoint could be reached. From our point of view the data were blinded, but informative (*cp. BfArM Scientific Advice Meeting Minutes 20090160 20 November 2014:* "BfArM asked Amgen why they were confident that the primary endpoint of erythroid response (ER) was likely to fail and the secondary endpoint would not. In response Amgen confirmed that the assumptions based on the review of the blinded data indicated that the ER rate could be much lower than the expected response rate of approximately 40% used to calculate the sample size for the study which was based on assumptions from the phase 2 study……Regarding accessing blinded raw data, BfArM asked why Amgen did not use simulated data for the task of preparing the TFL (tables, figures and listings) templates for the study report. In response Amgen confirmed that using actual blinded data with additional random inserted data is valuable to identify outliers and minimum and maximum values to support the preparation of the TFLs. This is common industry practice. BfArM acknowledged Amgen's transparency but confirmed that even though the data was blinded, it was informative and the decision to change the end point was therefore data driven."

Further, a usual reaction to a lower than anticipated response rate would have been to raise the sample size, but not to change the primary endpoint.

*But even if the unplanned analysis of the blinded data, would have had happened within the framework of an adaptive design, it is unlikely that it would have had been acceptable. The reflection paper states on page 7/10: "*Once the study is ongoing it is difficult to imagine any situation where the perception of what constitutes a relevant clinical benefit should change based on interim results, especially as primary endpoints are usually not selected to differentiate between treatment and control group. Furthermore, in a confirmatory setting, effects must always be attributable to specific endpoints to clarify the capabilities of the drug treatment.*" And ICH E9, page 8, sates: "*The primary variable should be specified in the protocol, along with the rationale for its selection. Redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess." *From our perception, the accidentally unintended detection, that the primary endpoint is very unlikely to be successful speaks for itself that there was enough information on the blinded data to trigger a change request for the protocol to establish more promising primary endpoint.*

After all, due to the change in the primary endpoint, there is a second chance for the trial to be successful.

***We consider this as a major flaw of the study**.*

Secondary Efficacy Endpoints

- achieving an IWG 2006 erythroid response during the double-blind treatment period

Secondary Safety Endpoints

- adverse events, including treatment-emergent adverse events of interest
- disease progression to AML through EOTP, EOATP, and LTFU
- malignancies other than AML, basal cell carcinoma, or squamous cell carcinoma of the skin through EOTP
- mortality through EOTP, EOATP, and LTFU
- neutralizing antibody formation to darbepoetin alfa at EOTP and EOATP

HRQOL endpoints

- change in patient-reported fatigue and overall health status from baseline to week 13, EOTP, week 31, week 42/43, week 54/55, and week 72/73/EOTP as measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and EuroQol-5D (EQ-5D)
- attaining a clinically meaningful change (3-point difference) in the FACIT-F subscale: improvement (at least a 3-point increase), deterioration (at least a 3-point decrease), or unchanged from baseline to EOTP (less than 3-point change in either direction)

Sample size

Other Countries than Germany (Protocol 4.0, p.59.):

A preliminary, blinded review of the first 80 subjects that reached EOTP in this study suggests that the pooled transfusion rate is approximately 48%. If a placebo transfusion rate of 67% is assumed, a

darbepoetin alfa rate of 38.5%, with a 2-sided significance level of 5% and a dropout rate of 5%, there would be 85% power to detect a difference in the transfusion rate from week 5 to EOTP if 141 subjects are randomised to achieve 135 evaluable subjects (software: nQuery Advisor 7.0).

Germany (Protocol 2.0, p. 60):

It is assumed that the response rate in the darbepoetin alfa group is 40%. If a placebo response rate of 10%, a 2-sided significance level of 5%, and a dropout rate of 15% are assumed, then there would be > 93% power to detect a difference in the proportion of subjects achieving a response based on the IWG 2006 erythroid response criteria during the double-blind treatment period if 141 subjects are randomised to achieve 122 evaluable subjects (software: nQuery Advisor version 7.0).

Biometrical comment

It is remarkable, that two different primary parameters with their own assumptions, result in the same number of patients to be randomized, namely 141.

Randomisation

Randomisation may occur on the same day as the first dose of investigational product (IP) (study day 1), or it may occur up to 4 days prior to study day 1 for purposes of obtaining IP from a central location or due to scheduling conflicts (ie, randomisation may occur on days -3, -2, -1, 0, or 1).

Eligible subjects were randomized to darbepoetin alfa or placebo in a 2:1 ratio via an IVRS:

1. darbepoetin alfa 500 µg Q3W
2. placebo Q3W

Randomisation was stratified by screening IPSS category (low versus intermediate-1). Randomisation was based on a schedule generated by Amgen before the start of the study and was centrally executed using an IVRS. The subject, site personnel, and Amgen study personnel and designees were blinded to the randomisation treatment group assignment. The investigator was unblinded to an individual subject's treatment assignment if the investigator deemed it necessary to break the blind in order to provide appropriate medical treatment for that subject.

Biometrical comment

The randomisation remains the same during the study. Nonetheless, the stratification on IPSS category is more relevant to the original primary endpoint.

Blinding (masking)

During the double-blind treatment period, the subject, site personnel, and Amgen study personnel and designees were blinded to subjects' randomized treatment assignments. The investigator was only unblinded to an individual subject's treatment assignment if the investigator deemed it necessary to provide appropriate medical treatment for that subject.

CHMP comment

The MAH should comment on when and how unblinding was performed after the DBTP.

Statistical methods

Primary analysis:

Countries except Germany

- (protocol p. 61) The proportion of subjects with at least 1 RBC transfusion from week 5 to EOTP will be analysed using a Chi-squared test for differences and using the CMH method stratified by the IPSS category (low versus intermediate-1). The analysis will be performed on subjects in the Transfusions from Week 5 to EOTP Primary Analysis Set.
- Statistical analysis plan (SAP-global, p.24): The primary efficacy endpoint, proportion of subjects with at least 1 RBC transfusion from week 5 to EOTP will be analyzed using a Chi-squared test for differences. The primary analysis will be done using the transfusion primary analysis set.

Germany

- (protocol p. 63): The primary efficacy endpoint, the proportion of subjects achieving the IWG erythroid response during the double-blind treatment period, will be analysed using the Cochran-Mantel-Haenszel (CMH) method stratified by the stratification factor, IPSS category (low versus intermediate-1). A subject will be considered a responder if he/she had the event (ie, achieved an initial ≥ 1.5 g/dL rise from baseline in haemoglobin level and sustained an average rise of ≥ 1.5 g/dL for at least 56 consecutive days) prior to withdrawing. A subject will be considered a non-responder if he/she did not meet these criteria prior to withdrawing. The primary analysis will be performed on the primary analysis set. Analysis of the primary endpoint will use central laboratory haemoglobin values. Subjects missing a central laboratory baseline haemoglobin value will be excluded from the analysis. Subjects will be considered non-responders if post-baseline haemoglobin data are not collected to the minimum time required to observe an IWG erythroid response; this minimum time is week 13 for subjects who adhere to the planned Q3W haemoglobin assessments (week 4 is the earliest time the initial 1.5 g/dL increase can occur that would then need to be sustained when the week 4 through 13 haemoglobin values are averaged).

- Germany SAP_Germany, p 24: The primary analysis of the erythroid response endpoint (proportion of subjects with a 1.5 g/dL increase in hemoglobin from baseline to EOTP, in the absence of RBC transfusions) will be performed on the primary analysis set. Analyses of the erythroid response endpoint will use central laboratory hemoglobin values. Subjects missing a central laboratory baseline hemoglobin value will be excluded from the analyses. Subjects will be considered non-responders if post-baseline hemoglobin data are not collected to the minimum time required to observe an IWG erythroid response; this minimum time is week 13 for subjects who adhere to the planned Q3W hemoglobin assessments (week 4 is the earliest time the initial 1.5 g/dL increase can occur that would then need to be sustained when the week 4through 13 hemoglobins are averaged in absence of RBC transfusion). The erythroid response endpoint will be summarized by treatment groups with associated 95% CIs. The difference between treatment groups will be assessed using the CMH method stratified by the randomization stratification factors (andby CRF stratification factors, if warranted). An analysis will be run in which the treatment groups differences will also be assessed using the Chi-Squared test for differences.

Biometrical comment

For the other countries than Germany the definition of the primary analysis differs between the protocol and the SAP. The analysis of the CMH method stratified by the IPSS category (low versus intermediate-1) is missing in the SAP. The exclusion of patients due to missing values or the declaration of non-responders may not be conservative. A scientific rationale is required.

For Germany the SAP defines an additional Chi-Squared test for difference. The exclusion of patients due to missing values or the declaration of non-responders may not be conservative. A scientific rationale is required.

Primary Analyses sets

Countries except Germany protocol (version 4)

- The primary analysis set will include all randomised and consented subjects who receive at least one dose of IP. Subjects will be analysed according to their randomized treatment assignment. Sensitivity analyses of the primary and secondary efficacy endpoints will be based on all randomised and consented subjects and a prospectively defined per-protocol analysis set.
- Transfusions from Week 5 to EOTP Primary Analysis Set: The Transfusions from Week 5 to EOTP Primary Analysis Set will include all subjects in the primary analysis set whose EOTP is ≥ day 29. The analysis of the primary endpoint, incidence of at least 1 RBC transfusion from week 5 to EOTP, will be performed using this analysis set.

SAP-global:

- All randomized and consented subjects who receive at least one dose of investigational product and who have an EOTP ≥ day 29 (ie, start of week 5). Subjects will be analyzed according to their randomized treatment group. The analysis of the incidence of at least 1 RBC transfusion from week 5 to EOTP, will be performed using this analysis set.
- Transfusion Per Protocol Set: The transfusion per protocol set will include all subjects in the Transfusion Primary Analysis Set who meet all the following criteria:
  - Low or intermediate-1 risk MDS per IPSS at randomization
  - No previous or ongoing use of ESA therapy at randomization
  - Not high transfusion demand patient as defined in the entry criteria
  - No RBC transfusions within 14 days prior to randomization
  - Serum endogenous EPO level ≤ 500 mU/mL at screening
  - No history of receiving biologic response modifiers or never received biologic response modifiers in the double-blind treatment period
  - Completed 6 doses in the double-blind treatment period (doses withheld per IVRS will count towards completion).

Germany (protocol, version 2, p60)

- The primary analysis set will include all randomised and consented subjects who receive at least one dose of IP. Subjects will be analysed according to their randomized treatment assignment. Sensitivity analyses of the primary and secondary efficacy endpoints will be based on all randomised and consented subjects and a prospectively defined per-protocol analysis set.

SAP-German, p 16

- The primary analysis set will include all randomized and consented subjects who receive at least one dose of investigational product. Subjects will be analyzed according to their randomized treatment group. If a subject has received investigational product which was different than their randomized treatment or any non-investigational product ESAs, they will still be analyzed according to their randomized treatment.

Biometrical comment

For the German protocol no per protocol set has been pre-defined.

Missing Data

Other Countries than Germany, SAP p.20:

Missing Transfusion Data:

- Subjects who withdraw from the double-blind treatment period prior to day 29 will have missing data for the incidence of RBC transfusions from week 5 to EOTP. These subjects will be excluded from the analysis of this endpoint.

Missing Hemoglobin Data for Change in Hemoglobin

- For the change in hemoglobin from baseline to EOTP endpoint, the last available post-baseline hemoglobin, not occurring in the 28 days after a RBC transfusion, will be used to calculate change in the event that the EOTP value is missing or occurred within 28 days after a RBC transfusion (last value carried forward approach; LVCF). Subjects without a post-baseline value that did not occur in the 28 days after a RBC transfusionand subjects with missing baseline hemoglobin will be excluded from the analysis of this endpoint.

Germany SAP-German, p.19

Handling of Missing and Incomplete Data

- Missing data for the primary and secondary efficacy endpoints, and key safety analyses will be investigated and every effort will be made to make sure data collected are complete and accurate. For laboratory test results, other than hemoglobin, the last value carried forward (LVCF) approach will be used for missing EOTP and EOATP measurements.

Missing Hemoglobin Data for IWG Erythroid Response

- Missing hemoglobin central laboratory data will not be imputed. Subjects missing a central laboratory baseline hemoglobin value will be excluded from the analysis of IWG erythroid response. Subjects will be considered non-responders if post-baseline hemoglobin data are not collected to the minimum time required to observe an IWG erythroid response; this minimum time is week 13 for subjects who adhere to the planned Q3W hemoglobin assessments (week 4 is the earliest time the initial 1.5 g/dL increase can occur that would then need to be sustained when the week 4 through 13 hemoglobin values get averaged).

Biometrical comment

Countries not including Germany:

It is not understood, why the exclusion of patients from the transfusion primary set is considered to be conservative. It would only be unbiased, if the patients with these missing values can be considered to be essentially the same as patients without missing values. For missing haemoglobin values it is not understood why this approach is considered to be conservative.

No sensitivity analysis using different handling of missing values are prespecified, but would had been expected.

Germany:

It is not understood, why the exclusion of patients from the primary set is considered to be

conservative. It would only be unbiased, if the patients with these missing values can be considered to be essentially the same as patients without missing values. For missing haemoglobin values it is not understood why this approach is considered to be conservative.

No sensitivity analysis using different handling of missing values are prespecified, but would had been expected.

Results

Participant flow

Table E9 Subject disposition in the DBTP

	Placebo (N = 49) n (%)	Darbepoetin alfa (N = 98) n (%)	Total (N = 147) n (%)
Subjects randomized	49 (100.0)	98 (100.0)	147 (100.0)
Investigational product accounting			
Subjects who never received investigational product	0 (0.0)	1 (1.0)	1 (0.7)
Subjects who received investigational product	49 (100.0)	97 (99.0)	146 (99.3)
Subjects who completed investigational product	39 (79.6)	87 (88.8)	126 (85.7)
Subjects continuing investigational product	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who discontinued investigational product	10 (20.4)	10 (10.2)	20 (13.6)
Ineligibility determined	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	1 (2.0)	0 (0.0)	1 (0.7)
Adverse event	2 (4.1)	2 (2.0)	4 (2.7)
Full consent withdrawn	2 (4.1)	3 (3.1)	5 (3.4)
Disease progression	0 (0.0)	0 (0.0)	0 (0.0)
Administrative Decision	0 (0.0)	1 (1.0)	1 (0.7)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	2 (4.1)	1 (1.0)	3 (2.0)
Protocol-specified criteria	1 (2.0)	2 (2.0)	3 (2.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Partial consent withdrawn	1 (2.0)	0 (0.0)	1 (0.7)
Other	1 (2.0)	1 (1.0)	2 (1.4)
Study completion accounting			
Subjects who completed DBTP	39 (79.6)	87 (88.8)	126 (85.7)
Subjects continuing study (enrolled in active treatment period)	39 (79.6)	87 (88.8)	126 (85.7)
Subjects continuing study (enrolled in long term follow up) [a]	4 (8.2)	6 (6.1)	10 (6.8)
Subjects who discontinued study	6 (12.2)	4 (4.1)	10 (6.8)
Ineligibility determined	0 (0.0)	0 (0.0)	0 (0.0)
Full consent withdrawn	3 (6.1)	3 (3.1)	6 (4.1)
Administrative Decision	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	2 (4.1)	1 (1.0)	3 (2.0)
Other	1 (2.0)	0 (0.0)	1 (0.7)

Page 1 of 1

[a]Subjects that did not participate in the active treatment period but went directly into long term follow up from the Double-blind Treatment Period.
Number of subjects screened: 226
First subject enrolled: 21DEC2011
Last subject completed follow-up: 18DEC2015

Table E10 Analysis Set disposition

	Placebo (N = 49) n (%)	Darbepoetin alfa (N = 98) n (%)	Total (N = 147) n (%)
Primary analysis set inclusion	49 (100.0)	97 (99.0)	146 (99.3)
Primary analysis set exclusion	0 (0.0)	1 (1.0)	1 (0.7)
Not consented	0 (0.0)	0 (0.0)	0 (0.0)
Did not receive at least 1 dose of IP	0 (0.0)	1 (1.0)	1 (0.7)
Transfusion primary analysis set inclusion	49 (100.0)	97 (99.0)	146 (99.3)
Transfusion primary analysis set exclusion	0 (0.0)	1 (1.0)	1 (0.7)
Excluded from primary analysis set	0 (0.0)	1 (1.0)	1 (0.7)
EOTP < day 29	0 (0.0)	0 (0.0)	0 (0.0)
Transfusion per protocol set inclusion	38 (77.6)	88 (89.8)	126 (85.7)
Transfusion per protocol set exclusion	11 (22.4)	10 (10.2)	21 (14.3)
Excluded from primary analysis set	0 (0.0)	1 (1.0)	1 (0.7)
Not low or intermediate risk MDS	0 (0.0)	0 (0.0)	0 (0.0)
Previous or ongoing ESA therapy at randomization	0 (0.0)	0 (0.0)	0 (0.0)
High transfusion demand defined by entry criteria	3 (6.1)	2 (2.0)	5 (3.4)
RBC transfusions within 14 days prior to randomization	1 (2.0)	2 (2.0)	3 (2.0)
Screening serum endogenous EPO >500 mU/mL	0 (0.0)	3 (3.1)	3 (2.0)
Ever received biologic response modifiers	0 (0.0)	0 (0.0)	0 (0.0)
Completed < 6 doses in the double-blind treatment period (doses withheld per IVRS will count towards completion).	9 (18.4)	7 (7.1)	16 (10.9)
HRQOL - FACIT analysis set inclusion	42 (85.7)	88 (89.8)	130 (88.4)
Fatigue Subscale[a] Analysis Set	42 (85.7)	90 (91.8)	132 (89.8)
Physical Well-Being Subscale[a] Analysis Set	42 (85.7)	89 (90.8)	131 (89.1)
Social Well-Being Subscale[a] Analysis Set	42 (85.7)	88 (89.8)	130 (88.4)
Emotional Well-Being Subscale[a] Analysis Set	42 (85.7)	89 (90.8)	131 (89.1)
Functional Well-Being Subscale[a] Analysis Set	42 (85.7)	90 (91.8)	132 (89.8)
HRQOL- EQ-5D VAS analysis set inclusion	42 (85.7)	90 (91.8)	132 (89.8)
HRQOL- EQ-5D Descriptive System analysis set inclusion	40 (81.6)	89 (90.8)	129 (87.8)
Safety analysis set inclusion	49 (100.0)	97 (99.0)	146 (99.3)
Safety analysis set exclusion	0 (0.0)	1 (1.0)	1 (0.7)
Not consented	0 (0.0)	0 (0.0)	0 (0.0)
Did not receive at least 1 dose of IP	0 (0.0)	1 (1.0)	1 (0.7)

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N=Number of subjects in the analysis set.
Note: Reasons for exclusion from an analysis set are not mutually exclusive.
[a]Greater than 50% of the subscale responses were missing and therefore not imputed.

CHMP comment

The MAH should also provide a tabulation of analysis sets with regard to the previous primary endpoint erythroid response, which is still valid in Germany.

Conduct of the study

Amendments

The protocol for this study (originally dated 25 March 2011) was amended 4 times. Major changes to the protocol are summarized in Table E11.

Protocol Amendment 3 (07 April 2014) was not implemented by all countries participating in the study. In Germany, after consultancy via a corresponding national scientific advice with the Rapporteur BfArM (cf. sections 1.1 and 2.4.2 above), erythroid response was retained as the primary endpoint and RBC

transfusion as a secondary endpoint.

Table E11 Protocol Amendments

Amendment	Major Changes
Original Protocol 25 March 2011	–
Amendment 1 17 October 2012 (61 subjects enrolled between this date and the date of the next amendment)	• Upper limits for blood pressure (≥ 160 mmHg systolic and ≥ 100 mmHg diastolic) were added to the screening eligibility criteria • Criteria for dosage adjustments and study withdrawal for subjects with severe or life-threatening adverse events were revised to provide guidance specific to uncontrolled blood pressure, hypertensive crisis, and thromboembolic events. • Added follow-up period (minimum of 3 years after the first dose of investigational product) to assess survival and progression to AML • Added secondary safety endpoint to assess the incidence of malignancies other than AML and basal cell or squamous cell carcinoma during the double-blind treatment period • Serious adverse event reporting was changed from 1 business day to 24 hours • Text regarding the assessment of expectedness for expedited reporting of safety events was updated
Superseding Amendment 1 17 October 2012	To comply with recent EMA guidance that revised the SAE reporting requirements from 1 business day to 24 hours.
Amendment 2 25 September 2013 (40 subjects enrolled between this date and the date of the next amendment)	• Reduced sample size from 180 to 141 subjects • The list of slides to be provided for central review for subjects with progression to AML was expanded to include peripheral blood smear specimens • Text was revised to clarify that central review for cases of progression to AML include the long-term follow-up period
Amendment 3 07 April 2014 (14 subjects enrolled between this date and the date of the next amendment)	• Revised the primary endpoint from IWG erythroid response during the double-blind treatment period to RBC transfusion from week 5 to the EOTP (previously the secondary endpoint); moved IWG erythroid response to a secondary endpoint
Amendment 4 10 August 2015 (3 subjects enrolled after this date)	• The primary transfusion endpoint was updated to be analyzed without adjusting for IPSS category. Evaluation of the transfusion endpoint stratified by IPSS category was included as a sensitivity analysis. • Hierarchical testing was removed since both endpoints were to be tested.
Superseding Amendment 4 10 August 2015	The text of the primary objective describing the period during which the incidence of RBC transfusions would be assessed was inadvertently changed in Amendment 4. A superseding amendment to Amendment 4 was created to revert back to the correct text.

CHMP comment

The primary endpoint was changed twice after 130 of 147 patients were enrolled.

Rationale for Amendment #3 as stated on the Amendment form: "Following an Amgen study team review of blinded data, the pooled IWG erythroid response rate appears too low for the study to meet its primary objective".

With Amendment #3 a sensitivity analysis at week 58 was introduced to evaluate the impact of dose

escalation after week 31. This was, however, again deleted with Amendment #4.

The MAH has not pointed to the superseding Amendments 1 and 4, neither the fact that Amendment 4 was dated 01 June 2015 instead of 10 August 2015.

Biometrical Comment:

The study required many amendments of the protocol as well as many amendments of the two distinct SAPs. This is considered below standard for a phase III study and casts doubt on a careful and robust planning of the study.

Protocol deviations / Quality assurance

The subject incidence of important protocol deviations was 17.3% in the darbepoetin group and 36.7% in the placebo group. The most frequently reported important protocol deviations were entry into the study despite a high transfusion demand before randomization (1.0% darbepoetin, 6.1% placebo), receiving IP after a temperature excursion (0% darbepoetin, 6.1% placebo), IVRS entry errors resulting in an underdose of investigational product (5.1% darbepoetin, 4.1% placebo), and a baseline central haemoglobin value not available per protocol (2.0% darbepoetin, 6.1% placebo).

Table E12 Enrolment Protocol Deviations

	Placebo (N=49) n(%)	Darbepoetin alfa (N=98) n(%)	Total (N=147) n(%)
Number of subjects with at least one enrollment protocol deviation	9 (18.4)	23 (23.5)	32 (21.8)
Entered study even though entry criteria not satisfied	9 (18.4)	23 (23.5)	32 (21.8)
Inclusion criteria	7 (14.3)	18 (18.4)	25 (17.0)
Assessment of IPSS greater than 16w of rand	3 (6.1)	5 (5.1)	8 (5.4)
Hb greater than 7 days prior rand	1 (2.0)	3 (3.1)	4 (2.7)
Serum folate or RBC folate out of range	0 (0.0)	4 (4.1)	4 (2.7)
Not low or Int-1 risk MDS per rand IPSS	0 (0.0)	3 (3.1)	3 (2.0)
Bone marrow within 16w of rand	2 (4.1)	1 (1.0)	3 (2.0)
Vitamin B12 less than 148 pmol/L during screening	0 (0.0)	3 (3.1)	3 (2.0)
Hb greater than 10 g/dL	1 (2.0)	1 (1.0)	2 (1.4)
Wrong WHO classification	0 (0.0)	1 (1.0)	1 (0.7)
Inadequate screen Tsat and/or ferritin	0 (0.0)	1 (1.0)	1 (0.7)
Exclusion criteria	6 (12.2)	8 (8.2)	14 (9.5)
High transfusion demand prior to rand	3 (6.1)	2 (2.0)	5 (3.4)
Transfusion within 14d prior to rand	1 (2.0)	2 (2.0)	3 (2.0)
Serum eEPO greater than 500mU/mL at screen	0 (0.0)	3 (3.1)	3 (2.0)
Dx or hx of malignancy other than MDS	1 (2.0)	1 (1.0)	2 (1.4)
Hx of thrombosis within 6 months prior to rand	0 (0.0)	1 (1.0)	1 (0.7)
Uncont hypertension at screen	1 (2.0)	0 (0.0)	1 (0.7)
Rcvd or plan to rcv cx prior to rand or in DBTP	0 (0.0)	1 (1.0)	1 (0.7)

According to the CSP study was not included in the independent Global Compliance Auditing program performed by Amgen.

CHMP comment

About 22% of patients violated the inclusion or exclusion criteria at enrolment, with 5% more violations in the darbepoetin group. Protocol deviations with regard to the disease under study, e.g., not low or int-1 MDS, vitamin B12 levels, Hb >10g/dl, high transfusion demand, or serum Epo <500mU/ml are considered balanced between the arms and have not favoured one or the other group.

No audit of the pivotal study was performed.

Baseline data

Overall, 54.8% of subjects were men, and all subjects were white. Demographics and baseline disease characteristics (Table E13) were comparable between treatment groups, with the exception of small differences in baseline WHO classification.

Table E13 Baseline demographics and disease characteristics (Primary Analysis Set)

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Total (N = 146)
Sex - n (%)			
Male	29 (59.2)	51 (52.6)	80 (54.8)
Female	20 (40.8)	46 (47.4)	66 (45.2)
Ethnicity - n (%)			
Hispanic/Latino	1 (2.0)	2 (2.1)	3 (2.1)
Not Hispanic/Latino	45 (91.8)	90 (92.8)	135 (92.5)
Unknown (French sites)[a]	3 (6.1)	5 (5.2)	8 (5.5)
Race - n (%)			
White	49 (100.0)	97 (100.0)	146 (100.0)
Age (years)			
n	49	97	146
Mean	72.4	72.4	72.4
SD	9.3	9.4	9.4
Median	73.0	74.0	74.0
Q1, Q3	66.0, 80.0	68.0, 79.0	67.0, 79.0
Min, Max	52, 88	28, 88	28, 88
Age group - n (%)			
< 65 years	10 (20.4)	15 (15.5)	25 (17.1)
≥ 65 years	39 (79.6)	82 (84.5)	121 (82.9)
≥ 75 years	22 (44.9)	47 (48.5)	69 (47.3)
≥ 85 years	5 (10.2)	3 (3.1)	8 (5.5)
IPSS risk category (IVRS) - n (%)			
Low	25 (51.0)	49 (50.5)	74 (50.7)
Intermediate-1	24 (49.0)	48 (49.5)	72 (49.3)
IPSS risk category (CRF) - n (%)			
Low	22 (44.9)	46 (47.4)	68 (46.6)
Intermediate-1	27 (55.1)	51 (52.6)	78 (53.4)
WHO Classification - n (%)			
RA	13 (26.5)	9 (9.3)	22 (15.1)
RARS	4 (8.2)	17 (17.5)	21 (14.4)
RCMD	19 (38.8)	45 (46.4)	64 (43.8)
MDS-U	1 (2.0)	1 (1.0)	2 (1.4)
MDS with Isolated Del (5q)	2 (4.1)	11 (11.3)	13 (8.9)
RAEB-1	10 (20.4)	13 (13.4)	23 (15.8)
RAEB-2	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (1.0)	1 (0.7)

Bone marrow blasts - n (%)			
<5%	40 (81.6)	83 (85.6)	123 (84.2)
5 to 10%	9 (18.4)	14 (14.4)	23 (15.8)
≥11%	0 (0.0)	0 (0.0)	0 (0.0)
Iron Stain - n (%)			
0	13 (26.5)	22 (22.7)	35 (24.0)
+1	9 (18.4)	18 (18.6)	27 (18.5)
+2	9 (18.4)	14 (14.4)	23 (15.8)
+3	4 (8.2)	17 (17.5)	21 (14.4)
+4	5 (10.2)	8 (8.2)	13 (8.9)
Missing[a]	9 (18.4)	18 (18.6)	27 (18.5)
Ringed Sideroblasts ≥ 15% - n (%)			
Yes	12 (24.5)	32 (33.0)	44 (30.1)
No	31 (63.3)	59 (60.8)	90 (61.6)
Missing	6 (12.2)	6 (6.2)	12 (8.2)

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Total (N = 146)
Karyotype (IPSS) - n (%)			
Good	44 (89.8)	89 (91.8)	133 (91.1)
Intermediate	5 (10.2)	8 (8.2)	13 (8.9)
Poor	0 (0.0)	0 (0.0)	0 (0.0)
Time since MDS Diagnosis to randomization (months)			
n	43	88	131
Mean	11.7	12.4	12.2
SD	17.6	16.7	16.9
Median	4.3	4.3	4.3
Q1, Q3	2.7, 12.6	2.0, 15.1	2.2, 14.5
Min, Max	1, 84	0, 75	0, 84
Hemoglobin (g/dL)			
n	35	75	110
Mean	9.10	9.23	9.19
SD	0.87	0.70	0.76
Median	9.30	9.30	9.30
Q1, Q3	8.80, 9.50	8.70, 9.80	8.80, 9.70
Min, Max	5.5, 10.6	7.6, 10.4	5.5, 10.6
Hemoglobin categories - n (%)			
≤8 g/dL	3 (6.1)	5 (5.2)	8 (5.5)
>8 to ≤9 g/dL	12 (24.5)	19 (19.6)	31 (21.2)
>9 to ≤10 g/dL	16 (32.7)	44 (45.4)	60 (41.1)
>10 g/dL	4 (8.2)	7 (7.2)	11 (7.5)
Unknown	14 (28.6)	22 (22.7)	36 (24.7)
Serum Endogenous EPO (mU/mL)			
n	49	97	146
Mean	132.83	111.36	118.57
SD	138.93	104.70	117.26
Median	73.50	66.10	68.60
Q1, Q3	35.80, 168.00	38.00, 150.00	35.90, 158.00
Min, Max	7.7, 497.0	4.3, 484.0	4.3, 497.0
Serum Endogenous EPO - n (%)			
<100 mU/mL	30 (61.2)	60 (61.9)	90 (61.6)
100 to 500 mU/mL	19 (38.8)	37 (38.1)	56 (38.4)
>500 mU/mL	0 (0.0)	0 (0.0)	0 (0.0)

IRON RELATED LABORATORY VALUES			
Serum Ferritin (µg/L)			
n	49	97	146
Mean	502.39	434.96	457.59
SD	476.67	401.21	427.56
Median	360.60	342.30	342.95
Q1, Q3	162.60, 606.60	160.00, 574.40	160.00, 598.20
Min, Max	17.6, 2364.3	16.3, 2332.2	16.3, 2364.3
Serum Ferritin (µg/L) - n (%)			
<40	1 (2.0)	5 (5.2)	6 (4.1)
≥40 to <200	13 (26.5)	26 (26.8)	39 (26.7)
≥200 to <1000	29 (59.2)	59 (60.8)	88 (60.3)
≥1000	6 (12.2)	7 (7.2)	13 (8.9)
Tsat (%)			
n	45	90	135
Mean	53.0	54.9	54.3
SD	24.2	21.5	22.4
Median	50.0	52.0	51.0
Q1, Q3	33.0, 69.0	41.0, 74.0	37.0, 73.0
Min, Max	9, 95	11, 96	9, 96

Table E14 Transfusion History

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Total (N = 146)
Overall RBC transfusions in the 16 weeks prior to randomization – n (%)			
0 units	26 (53.1)	59 (60.8)	85 (58.2)
1 to 2 units	8 (16.3)	18 (18.6)	26 (17.8)
3 to 4 units	8 (16.3)	14 (14.4)	22 (15.1)
5 to 6 units	5 (10.2)	6 (6.2)	11 (7.5)
>6 units	2 (4.1)	0 (0.0)	2 (1.4)
RBC transfusions in first 8 of 16 weeks prior to randomization (days -113 to -57) – n (%)			
0 units	33 (67.3)	76 (78.4)	109 (74.7)
1 unit	2 (4.1)	6 (6.2)	8 (5.5)
2 units	9 (18.4)	15 (15.5)	24 (16.4)
3 units	3 (6.1)	0 (0.0)	3 (2.1)
>3 units	2 (4.1)	0 (0.0)	2 (1.4)
RBC transfusions in second 8 of 16 weeks prior to randomization (days -56 to 0) – n (%)			
0 units	28 (57.1)	64 (66.0)	92 (63.0)
1 unit	3 (6.1)	6 (6.2)	9 (6.2)
2 units	12 (24.5)	15 (15.5)	27 (18.5)
3 units	4 (8.2)	10 (10.3)	14 (9.6)
>3 units	2 (4.1)	2 (2.1)	4 (2.7)
Hemoglobin at time of RBC transfusion[a] – n (%)			
<7 g/dL	3 (6.1)	2 (2.1)	5 (3.4)
7 to <8 g/dL	8 (16.3)	10 (10.3)	18 (12.3)
8 to <9 g/dL	11 (22.4)	19 (19.6)	30 (20.5)
9 to ≤10 g/dL	1 (2.0)	6 (6.2)	7 (4.8)
>10 g/dL	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (1.0)	1 (0.7)
Never transfused	26 (53.1)	59 (60.8)	85 (58.2)

The most frequently reported baseline medical history overall were hypertension (57.7% darbepoetin vs. 49.0% placebo), diabetes mellitus (17.5% darbepoetin vs. 20.4% placebo), and coronary artery disease (13.4% darbepoetin vs. 14.3% placebo).

CHMP comment

Overall, baseline demographics were balanced between the arms. About 80-85%% of patients were ≥65 years, ~ 43% ≥75 years. All patients were white and about 55% were male. According to IVRS, IPSS scores were equal for low and int-1 MDS with 92% good karyotype. Mean time since MDS diagnosis to randomisation was 12 months.

Baseline differences for WHO classifications are noted (plc. vs darb.): 26.5 vs. 9.3% RA, 8.2 vs. 17.5% RARS, 38.8 vs. 46.4% RCMD, 20.4 vs. 13.4% RAEB-1, 4.1 vs. 11.3% del5qMDS. Isolated del5q is known to have the best prognosis, followed be a comparable good prognosis of RA and RARS, RAEB has the worst prognosis of the eligible MDS classes. However, the differences noted are considered not having introduced bias between the treatment arms.

Mean Hb at baseline was 9.2g/dl, with 5.5% below 8g/dl and 21% between 8-9g/dl. For Hb >9-≤10g/dl an imbalance is noted with 32.7 vs. 45.4% plc. vs. darb. which could have favoured the darbepoetin arm.

58% received no transfusions in the 16 weeks prior to randomisation. More patients in the placebo arm received 3 and more units RBC in the 16 weeks prior to randomisation (30.6% vs. 20.6%).

Endogenous Epo levels were low in the study population with mean of 118.6mU/ml and a 3rd quartile of 158mU/ml. Thus, 62% in both arms had levels <100mU/ml. The MAH should give details about number of patients with Epo levels <200mU/ml.

Differences in concomitant medical conditions of about 9-10% are noted for hypertension, myocardial infarction (14.3 vs. 4.1%) and cardiac arrhythmia (11.3 vs. 2.0%, plc. vs. darbepoetin, resp.).

Overall, it is considered that the study population of the pivotal study reflects an ESA-naïve patient population sufficiently well. However, the intended indication is only in part reflected by the study population, as no ESA-pretreated patients were included. Thus, a B/R assessment based on confirmatory data can only be performed for these ESA-naïve patients, whereas a B/R evaluation for ESA-pretreated patients with hence more refractory anaemia needs to be based on the only descriptive results of the phase II study 20030207.

Outcomes and estimation

Primary endpoint

The incidence of RBC transfusion from week 5 to EOTP was statistically significantly lower in the darbepoetin alfa group (36.1%) than in the placebo group (59.2%), p = 0.008.

Table E15 Study 20090160 RBC Transfusions from week 5 to EOTP

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Treatment Difference
Subjects With RBC Transfusion from Week 5 to EOTP (Transfusion Primary Analysis Set)			
Subjects transfused - n (%)	29 (59.2)	35 (36.1)	
Unadjusted analysis[a] p-value			0.008

Similar results were observed in a sensitivity analysis of RBC transfusions from week 1 to the EOTP and further sensitivity analyses, as listed in table E16.

Table E16 Sensitivity Analyses: Subjects with RBC Transfusions

	Placebo	Darbepoetin alfa	Treatment Difference
Subjects With RBC Transfusion from Week 1 to EOTP (Primary Analysis Set)			
N	49	97	
Subjects transfused - n (%)	31 (63.3)	39 (40.2)	
Unadjusted analysis[a] p-value			0.008
Subjects transfused or with hemoglobin ≤ 8.0 g/dL who did not receive an RBC transfusion (Transfusion Primary Analysis Set)			
N	49	97	
Subjects transfused or with hemoglobin ≤ 8.0 g/dL - n (%)	32 (65.3)	39 (40.2)	
Unadjusted analysis[a] p-value			0.004
Subjects transfused (limited to those administered when hemoglobin level was ≤ 8.0 g/dL) (Transfusion Primary Analysis Set)			
N	49	97	
Subjects transfused - n (%)	21 (42.9)	24 (24.7)	
Unadjusted analysis[a] p-value			0.025
Subjects With RBC Transfusion from Week 5 to EOTP (Transfusion Per Protocol Analysis Set)			
N	38	88	
Subjects transfused - n (%)	19 (50.0)	31 (35.2)	
Unadjusted analysis[a] p-value			0.120

[a] Two-sided Chi-square test

IPSS Category- n_i/n_{ij}(%: 95% CI)				
Low	12/25 (48.0: 27.80, 68.69)	16/49 (32.7: 19.95, 47.54)	0.53 (0.20, 1.41)	
Intermediate - 1	17/24 (70.8: 48.91, 87.38)	19/48 (39.6: 25.77, 54.73)	0.27 (0.09, 0.77)	
Overall[a]			0.38 (0.19, 0.79)	0.008
Baseline hemoglobin - n_i/n_{ij}(%: 95% CI)				
≤8 g/dL	3/3 (100.0: 29.24, 100.00)	4/5 (80.0: 28.36, 99.49)	NE (NE, NE)	
>8 to ≤9 g/dL	8/12 (66.7: 34.89, 90.08)	6/19 (31.6: 12.58, 56.55)	0.23 (0.05, 1.08)	
>9 to ≤10 g/dL	6/16 (37.5: 15.20, 64.57)	5/44 (11.4: 3.79, 24.56)	0.21 (0.05, 0.85)	
>10 g/dL	0/4 (0.0: 0.00, 60.24)	2/7 (28.6: 3.67, 70.96)	NE (NE, NE)	
Overall[a]			0.30 (0.11, 0.76)	0.011

In an analysis adjusting for treatment, history of transfusions, and baseline haemoglobin, the number of RBC units transfused from week 5 to the EOTP was lower in the darbepoetin arm (2.6 units; 95% CI: 1.8, 3.4) than in the placebo arm (4.1 units; 95% CI: 3.0, 5.3) (p = 0.038).

The number of episodes of RBC transfusion from week 5 to EOTP in the adjusted analysis also was lower in the darbepoetin arm (0.1 episodes; 95% CI: -0.1, 0.3) than in the placebo arm (0.6 episodes; 95% CI: 0.4, 0.8) (p < 0.001). Consistent results were observed for the number units transfused and the number of episodes of RBC transfusion from week 1 to the EOTP.

CHMP comment

The incidence of RBC transfusion from week 5 to EOTP was statistically significantly lower in the darbepoetin alfa group (36.1%) than in the placebo group (59.2%), p = 0.008.

Interpretation need to take into account, that randomisation was not stratified for the degree of transfusion need and apparently more patients with a higher transfusion need were randomised to the placebo arm.

Notably, in the Per Protocol Set and the IPSS Low category no significant efficacy was established with regard to transfusion reduction for darbepoetin against placebo; neither for patients with Hb <8g/dl as 3/3 and 4/5 needed transfusions, though this is based on small numbers.

No detailed transfusion results could be found for the primary analysis splitted for endogenous serum baseline epo levels or WHO classes. This should be provided. For endogenous epo, an additional subgroup analysis for epo levels <200/≥200mU/ml is requested for RBC transfusions.

Neither results could be found about time to first RBC / TT first RBC after week 5 – also K-M curves are requested.

Primary Outcome - Germany

Table 10-3. IWG 2006 Erythroid Response in the Double-blind Treatment Period (IVRS Strata) (Primary Analysis Set)

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Treatment Difference (OR: 95% CI)
Subjects evaluable[a] - n	35	75	
Low IPSS risk category	18	38	
Intermediate-1 IPSS risk category	17	37	
Non-responders - n (%)	35 (100.0)	64 (85.3)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 10.00)	11 (14.7: 7.56, 24.73)	(NE: NE, NE)
p-value[c]			0.016
Response by baseline IPSS category			
Low IPSS risk category			
Non-responders - n (%)	18 (100.0)	31 (81.6)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 18.53)	7 (18.4: 7.74, 34.33)	(NE: NE, NE)
p-value[d]			0.054
Intermediate-1 IPSS risk			
Non-responders - n (%)	17 (100.0)	33 (89.2)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 19.51)	4 (10.8: 3.03, 25.42)	(NE: NE, NE)
p-value[d]			0.16
p-value[e]			0.017

N = Number of subjects in the analysis set. CI=Confidence Interval. NE=not estimable.
[a] Subjects missing a central laboratory baseline hb value are not included in the analysis.
[b] Response is an initial ≥1.5 g/dL increase from baseline hb and sustaining an average increase of ≥1.5 g/dL in a rolling 56-consectutive day period in the absence of RBC transfusions (Cheson et al 2006).
[c] p-value is from Fisher's exact test.
[d] p-value is from a 2-sided Cochran-Mantel-Haenszel (CMH) test by strata.
[e] The overall 2-sided CMH test with IPSS score as stratification factor.

Program: /userdata/stat/nesp/onc/nesp20090160/analysis/primary/tables/t-ery-resp.sas
Output: t14-04-006-001-ery-resp-db.rtf (Date Generated: 10FEB2016:07:28) Source Data: libcrt.keyvar, libcrt.eendpt

The proportion of subjects achieving an IWG 2006 erythroid response during the double-blind treatment period was statistically significantly greater in the darbepoetin alfa group (14.7%) than in the placebo group (0%), p = 0.016 (Table 10-3).

All subjects with erythroid response (n = 11) had a baseline serum endogenous EPO level of <100mU/mL.

Biometrical comment:

It remains open if the monitoring for the primary endpoint was identical for Germany and the other countries.

For both primary analyses the exclusion of patients is quite pronounced. No sensitivity analysis has been provided for a conservative approach of imputation of missing values. Due to the high patient loss in the primary sets, a thorough discussion of bias should be delivered. For each SAP, the patient

set, that were excluded from the primary analysis should be compared to the patient set that contributed to the primary analyses in respect to at least the following measures: baseline demographics and disease characteristics, county and safety measures. Further, a sensitivity analysis based on more relaxed responder criteria, e.g. IWG 2000) is considered helpful.

A detailed description of measures planned to avoid missing values and how they were followed.

Secondary efficacy endpoint IWG 2006 erythroid response

(same as Primary outcome – Germany above)

IWG 2006 erythroid response was defined as achieving an initial ≥1.5 g/dL increase in haemoglobin from baseline and sustaining an average rise of ≥1.5 g/dL in a rolling 56-consecutive day (=8-week) period in the absence of RBC transfusion.

The proportion of subjects achieving an IWG 2006 erythroid response during the double-blind treatment period was statistically significantly greater in the darbepoetin group (14.7%) than in the placebo group (0%), p = 0.016 (Table E17).

All subjects with erythroid response (n = 11) had a baseline serum endogenous EPO level of <100 mU/mL.

Table E17 IWG 2006 Erythroid response in the DBTP (IVRS Strata)

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	Treatment Difference (OR: 95% CI)
Subjects evaluable[a] - n	35	75	
Low IPSS risk category	18	38	
Intermediate-1 IPSS risk category	17	37	
Non-responders - n (%)	35 (100.0)	64 (85.3)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 10.00)	11 (14.7: 7.56, 24.73)	(NE: NE, NE)
p-value[c]			0.016
Response by baseline IPSS category			
Low IPSS risk category			
Non-responders - n (%)	18 (100.0)	31 (81.6)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 18.53)	7 (18.4: 7.74, 34.33)	(NE: NE, NE)
p-value[d]			0.054
Intermediate-1 IPSS risk			
Non-responders - n (%)	17 (100.0)	33 (89.2)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 19.51)	4 (10.8: 3.03, 25.42)	(NE: NE, NE)
p-value[d]			0.16
p-value[e]			0.017

N = Number of subjects in the analysis set. CI=Confidence Interval. NE=not estimable.
[a] Subjects missing a central laboratory baseline hb value are not included in the analysis.
[b] Response is an initial ≥1.5 g/dL increase from baseline hb and sustaining an average increase of ≥1.5 g/dL in a rolling 56-consectutive day period in the absence of RBC transfusions (Cheson et al 2006).
[c] p-value is from Fisher's exact test.
[d] p-value is from a 2-sided Cochran-Mantel-Haenszel (CMH) test by strata.
[e] The overall 2-sided CMH test with IPSS score as stratification factor.

CHMP comment

Only 75 of 97 (darbepoetin) and 35 of 49 (placebo) patients were evaluable for the "IWG 2006 Erythroid Response in the Double-blind Treatment Period" secondary endpoint (= German primary EP), because patients without central baseline Hb values were counted not evaluable. (Note: the 22 and 14 unevaluable patients occur as "Hb category unknown" in the demographic table). It is stated in the study protocol that at each visit a local Hb lab should have been performed in addition to complete blood count including Hb by the central lab, which might have mislead the investigators. The MAH should provide a sensitivity analysis utilising local baseline Hb values for the missing patients, if available. See also biometrical comment above.

As all patients with (evaluated) erythroid response (11 of 97 treated with darbepoetin) were in the group of <100mU/ml endogenous EPO safety should be analysed also for these subgroups; see also safety assessment below. In addition, as after a "conservative approach of imputation of missing values" and/or including the a.m. local labs' Hb additional responders with endogenous Epo of <200mU/ml may become evident, safety results should in addition be subdivided by

<200/≥200 mU/ml.

The details of erythroid response according to baseline Hb-subgroups and WHO classification should be submitted and/or additionally performed, as these represent important prognostic factors. Also time to response and duration of response should be evaluated.

The small number of erythroid responders (14.7%) in the pivotal phase III raises the concern that the fixed dose of 500µg darbepoetin Q3W SC during the DBTP was too low, as percentages of responders were much lower than in earlier studies (e.g., study 20030207 40% -the basis for the primary sample size calculation-, or as summarized in the pivotal CSP Appendix F) and in a comparable study population with epoetin alpha (27%) which led to approval of an MDS indication earlier this year.

During the double-blind period patients had an average darbepoetin dose of 148.5µg/week, or weight-adjusted 2.0µg/kg/week.

The applicant is asked to discuss reasons for these obvious differences in responses in view of dosing recommendations.

Analyses for Germany

In the analyses for Germany, erythroid response was analysed as the primary efficacy endpoint and RBC transfusion as the secondary efficacy endpoint. As darbepoetin was statistically superior to placebo at the 5% level with respect to the primary erythroid response endpoint (p = 0.016), the secondary RBC transfusion endpoint was formally tested. The results were the same as those presented above.

CHMP comment

The here presented paragraph is the information that is provided in the CSP with regard to the change of primary and secondary endpoints. This minimal information and results presented as the "analysis for Germany" are considered inadequate. See also biometrical comments.

Secondary HQRL endpoints

Mean (SD) FACIT-Fatigue (FACIT-F) scores at baseline were similar between the darbepoetin group (33.1 [11.4] points) and placebo group (32.9 [11.4] points).

The change in mean (SD) FACIT-F score showed an increase (ie, improvement) of 1.1 (8.8) points in the darbepoetin group and a decrease of 0.5 (7.1) points in the placebo group during the double-blind treatment period.

No improvement was observed in either treatment group on the FACIT Physical Well-being, Social/Family Well-being, Emotional Well-being, or Functional Well-being subscales during the double-blind treatment period.

On the FACIT-Overall, the mean (SD) score decreased from baseline to EOTP by 0.7 (19.1) points in the darbepoetin group and 4.1 (17.2) points in the placebo group.

No significant difference in the percentage of subjects with a clinically meaningful (≥ 3-point) improvement in FACIT-F subscale score during the double-blind treatment period was observed between the darbepoetin group (35.6%and the placebo group (31.0%).

Table E18 Clinically meaningful improvement in FACIT-Fatigue subscale during the DBTP

	Placebo (N = 42)	Darbepoetin alfa (N = 90)	Odds Ratio (95% CI)
Subjects evaluable - n[a]	42	90	
Change in FACIT-F subscale - n (%: 95% CI)			
Clinically meaningful improvement (≥ 3)	13 (31.0: 17.62, 47.09)	32 (35.6: 25.74, 46.35)	1.23 (0.56, 2.69)
Unchanged (-3 to 3)	15 (35.7: 21.55, 51.97)	28 (31.1: 21.77, 41.74)	0.81 (0.38, 1.76)
Deterioration (≤ -3)	14 (33.3: 19.57, 49.55)	30 (33.3: 23.74, 44.05)	1.00 (0.46, 2.17)
p-value from test for a treatment difference[b]			0.60

N = Number of subjects in the analysis set. CI=Confidence Interval.
[a] Subjects missing a post-baseline FACIT-Fatigue score are not included in the analysis.
[b] P-value is from a 2-sided Cochran-Mantel-Haenszel test of the proportion of subjects with clinically meaningful improvement (ie, ≥3 versus <3) with IVRS IPSS score as stratification factor.

Across treatment groups, greater increases in haemoglobin were associated with greater improvements in FACIT-F score at week 25, although the number of subjects with haemoglobin increases >1.0 g/dL were small.

Table 19 Change in FACIT-Fatigue scores by change in Hb at Week 25

	Hb Change <0 g/dL (N = 32)	Hb Change 0 to <1g/dL (N = 30)	Hb Change 1 to <1.5g/dL (N = 7)	Hb Change >=1.5g/dL (N = 11)	Total (N = 80)
Change from Baseline to Week 25					
n	32	29	7	10	78
Mean	0.59	1.04	6.14	6.46	2.01
SD	8.51	7.13	10.43	7.78	8.27
Median	0.00	0.00	4.00	4.50	0.50
Q1, Q3	-4.50, 6.00	-3.00, 7.00	0.00, 8.00	1.00, 8.00	-3.00, 7.00
Min, Max	-23.0, 20.0	-10.0, 18.0	-4.0, 28.0	-3.0, 23.6	-23.0, 28.0

N = Number of subjects in the analysis set. n=Number of subjects with observed data.
Subjects must have baseline and post-baseline FACIT-Fatigue score and hemoglobin to be included in the analysis.

The mean (SD) change from baseline to EOTP on the EQ5D-VAS was 2.1 (13.1) points in the darbepoetin group and 0.8 (15.7) points in the placebo group.

CHMP comment

No clinically relevant changes to baseline were observed in HQRL scales FACIT overall, FACIT-F or EQ5D in the full (FACIT-Fatigue) analysis set during the DBTP.

In view of QoL as one of the two main treatment goals in lower-risk MDS patients, as discussed e.g. in the ESMO clinical practice guidelines in 2014, darbepoetin has not shown efficacy for this endpoint and hence no benefit in the total study population.

At least, a clinically meaningful improvement in FACIT-F scores (>6) was observed in "erythroid responders" (here Hb change ≥1g/dl) at week 25, though observed in small subgroups (n=7 and n=11) only. This is in agreement with the results from the phase II study and also with results from a published randomized phase III study with epoetin in lower-risk MDS patients where improvements in QoL were also limited to patients with an erythroid response (Greenberg et al. 2009).

In conclusion, QoL improvements, which are considered a significant benefit in lower-risk MDS patients, were not established to be improved with the tested Q3W 500µg darbepoetin treatment in non-responders in the DBTP of the pivotal study.

Other endpoint: anti-darbepoetin antibodies

Serum samples for the evaluation of anti-darbepoetin alfa antibodies were to be collected before administration of the first dose of investigational product, at EOATP, and at EOTP. A total of 97 subjects in the darbepoetin group and 46 subjects in the placebo group had a pre-dose antibody result (i.e., taken before administration of investigational product); 91 subjects and 43 subjects, respectively, had a post-dose antibody result. Despite positive results on the binding assay during the study (2.0% darbepoetin alfa, 2.1% placebo), no sample tested positive in the bioassay for neutralizing antibodies.

CHMP comment

Although nearly all of the study patients had anti-darbepoetin antibodies at baseline, i.e. prior to having been treated with an ESA according to exclusion criterion 4.2.13), or during the study, no neutralizing antibodies were detected.

However, the MAH should comment on the sensitivity of the assay as in 143 patients antibodies were detected, although they were included as without any prior ESA-treatment.

Ancillary analyses

With a separate Supplemental CSR, dated 26 August 2016, the results of an interim analysis of study 20090160 were submitted.

Study endpoints in the interim analysis included the following:

- incidence of at least 1 RBC transfusion from week 5 to EOATP and week 1 to EOATP
- achieving an IWG 2006 erythroid response from week 25 to EOATP and study day 1 to EOATP
- adverse events, including treatment-emergent adverse events of interest, from week 25 to EOATP
- disease progression to AML from week 25 to EOATP and study day 1 to EOATP
- malignancies other than AML, basal cell carcinoma, or squamous cell carcinoma of the skin from week 25 to EOATP and study day 1 to EOATP
- mortality from study day 1 to EOATP
- neutralizing antibody formation to darbepoetin alfa at EOATP from week 25 to EOATP and from study day 1 to EOATP
- change in patient-reported fatigue and overall health status from study day 1 during the active treatment period as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and EuroQol-5D (EQ-5D)

Statistical methods

The analyses of selected efficacy and safety endpoints for the active treatment period (and the double-blind and active treatment periods combined), were performed after all subjects had either completed the EOATP (week 72/73, or 3 weeks after the last dose of darbepoetin alfa Q3W or 2 weeks after the last dose of darbepoetin alfa Q2W) or withdrawn from study, and after those data were retrieved,

entered, and cleaned.

Results

Participants

Subjects in both treatment groups received darbepoetin during the active treatment period.

Note: In the following, the previous placebo-treated patients will still be named “placebo”.

After completing the 24-week double-blind, placebo-controlled treatment period, 126 subjects originally randomized to darbepoetin alfa (n = 87 of 98) or placebo (n = 39 of 48) entered the active treatment period of the study.

Twenty-eight subjects (32.2%) in the darbepoetin-darbepoetin alfa group and 13 subjects (33.3%) in the placebo-darbepoetin group who entered the active treatment period discontinued investigational product.

Efficacy results

The incidence of RBC transfusions from week 5 of the double-blind treatment period to EOATP (which included the active treatment period in which all subjects received darbepoetin) was 60.3% (59.8% in the darbepoetin-darbepoetin group and 61.5% in the placebo-darbepoetin group) (Table E20). In both treatment groups, a higher proportion of subjects who remained on Q3W dosing had a transfusion from Week 5 to EOATP than those who their dose adjusted to Q2W.

Table E20 Subjects in the active treatment period with RBC Transfusions from week 5 to EOATP

	Placebo (N = 39)	Darbepoetin alfa (N = 87)	Treatment Difference
Subjects transfused - n (%)	24 (61.5)	52 (59.8)	
Unadjusted analysis[a]			
p-value			0.85
Subjects with only Q3W Dosing	7	17	
Subjects transfused - n (%)	5 (71.4)	11 (64.7)	
Subjects with some Q2W Dosing	32	70	
Subjects transfused - n (%)	19 (59.4)	41 (58.6)	

N = Number of subjects in the analysis set. n=Number of subjects in the analysis set with observed data
[a]Two-sided Chi-square test for descriptive purposes only.

CHMP comment

This and the following analysis counting transfusions from start of the double blind phase until end of open-label phase are considered quite non-informative. The MAH should provide and discuss data for transfusions and erythroid responses only for the open label phase to be able to compare effects of dosing regimens.

126 subjects originally randomized to darbepoetin alfa (n = 87 of 98) or placebo (n = 39 of 48) entered the active treatment period of the study. From the provided data obtained after the open label phase 79% of the darbepoetin patients and 82% of the placebo patients increased their doses from Q3W to Q2W dosing scheme. For the darbepoetin group this is another important demonstration of a too low dosing during the blinded phase up to the primary endpoint.

During the active treatment period, patients who remained with Q3W dosing had an average darbepoetin dose of 143µg/week (ex-plc) or 131µg/week (ex-darb), which corresponds to weight-based 2.1µg/kg/week or 1.7µg/kg/week, respectively.

Patients who increased doses to Q2W had an average dose of 204µg/week (both groups), corresponding to 2.85µg/kg/week (both groups).

Of cause, it is noted that patients who have left the double-blind phase early due to too low dosing could not contribute to this dosing evaluation, which also means that the dose really necessary might still be higher than this.

Patients who remained on the Q3W scheme had more transfusions than those who switched. And for both, the previous placebo and the previous darbepoetin patients, the frequency of transfusions under Q2W dosing was identical with 59%.

*The following planned analysis was deleted with Amendment#4: "*For the subgroup of subjects who receive a dose escalation to 500 µg Q2W during the active treatment period, summary statistics will be generated for selected haemoglobin, transfusion, and safety endpoints in order to explore the impact of the dose adjustment." *The MAH should reinitiate to evaluate all the mentioned points, and include time of dose change, further dose adjustments, e.g. due to excessive Hb increase.*

Table E21 Sensitivity Analyses RBC Transfusions

	Placebo	Darbepoetin alfa	Treatment Difference
Subjects With RBC Transfusion from Week 1 to EOATP (Primary Analysis Set)			
N	39	87	
Subjects transfused - n (%)	26 (66.7)	53 (60.9)	
Unadjusted analysis[a] p-value			0.54
Subjects transfused from Week 5 to EOATP or with hemoglobin ≤ 8.0 g/dL (Transfusion Primary Analysis Set)			
N	39	87	
Subjects transfused or with hemoglobin ≤ 8.0 g/dL - n (%)	26 (66.7)	53 (60.9)	
Unadjusted analysis[a] p-value			0.54
Subjects transfused from Week 5 to EOATP (limited to those administered when hemoglobin level was ≤ 8.0 g/dL) (Transfusion Primary Analysis Set)			
N	39	87	
Subjects transfused - n (%)	20 (51.3)	39 (44.8)	
Unadjusted analysis[a] p-value			0.50
Subjects With RBC Transfusion from Week 5 to EOATP (Transfusion Per Protocol Analysis Set)			
N	37	85	
Subjects transfused - n (%)	22 (59.5)	51 (60.0)	
Unadjusted analysis[a] p-value			0.96

[a] Two-sided Chi-square test

The mean (SE) number of episodes of RBC transfusion from week 5 to EOATP was 5.1 (0.8) episodes in the darbepoetin-darbepoetin group and 5.7 (1.2) episodes in the placebo-darbepoetin group.

IWG 2006 erythroid response

The proportion of subjects who achieved an IWG 2006 erythroid response during the active treatment period (from week 25 to the EOATP) was 34.7% (33.3% in the darbepoetin-darbepoetin group and 37.9% in the placebo-darbepoetin group.

Table E22 IWG 2006 erythroid response in the active treatment period: a) all dosing schemes, b) Q3W dosing only, c) incl. Q2W dosing

a) all dosing schemes

	Placebo (N = 39)	Darbepoetin alfa (N = 87)	Treatment Difference (OR: 95% CI)
Total			
Subjects evaluable[a] - n	29	69	
Low IPSS risk category	15	34	
Intermediate-1 IPSS risk category	14	35	
Non-responders - n (%)	18 (62.1)	46 (66.7)	
Responders[b] - n (%: 95% CI)	11 (37.9: 20.69, 57.74)	23 (33.3: 22.44, 45.71)	(0.82: 0.33, 2.02)
p-value[c]			0.66
Response by baseline IPSS category			
Low IPSS risk category			
Non-responders - n (%)	8 (53.3)	22 (64.7)	
Responders[b] - n (%: 95% CI)	7 (46.7: 21.27, 73.41)	12 (35.3: 19.75, 53.51)	(0.62: 0.18, 2.14)
p-value[d]			0.46
Intermediate-1 IPSS risk			
Non-responders - n (%)	10 (71.4)	24 (68.6)	
Responders[b] - n (%: 95% CI)	4 (28.6: 8.39, 58.10)	11 (31.4: 16.85, 49.29)	(1.15: 0.29, 4.47)
p-value[d]			0.85
p-value[e]			0.68

CI = confidence interval; N = number of subjects in the analysis set; NE = not estimable
[a] Subjects missing a central laboratory baseline hb value are not included in the analysis.
[b] Response is an initial ≥1.5 g/dL increase from baseline hb and sustaining an average increase of ≥1.5 g/dL in a rolling 56-consecutive day period in the absence of RBC transfusions (Cheson et al 2006).
[c] p-value is from Chi-square or Fishers exact test if sample size low.
[d] p-value is from a 2-sided Cochran-Mantel-Haenszel (CMH) test by strata.
[e] The overall 2-sided CMH test with IPSS score as stratification factor.

b) Q3W dosing only

	Placebo (N = 39)	Darbepoetin alfa (N = 87)	Treatment Difference (OR: 95% CI)
Subjects with only Q3W Dosing			
Subjects evaluable[a] - n	4	9	
Low IPSS risk category	3	4	
Intermediate-1 IPSS risk category	1	5	
Non-responders - n (%)	3 (75.0)	6 (66.7)	
Responders[b] - n (%: 95% CI)	1 (25.0: 0.63, 80.59)	3 (33.3: 7.49, 70.07)	(1.50: 0.11, 21.31)
p-value[c]			1.00
Response by baseline IPSS category			
Low IPSS risk category			
Non-responders - n (%)	2 (66.7)	1 (25.0)	
Responders[b] - n (%: 95% CI)	1 (33.3: 0.84, 90.57)	3 (75.0: 19.41, 99.37)	(6.00: 0.22, 162.53)
p-value[d]			0.31
Intermediate-1 IPSS risk			
Non-responders - n (%)	1 (100.0)	5 (100.0)	
Responders[b] - n (%: 95% CI)	0 (0.0: 0.00, 97.50)	0 (0.0: 0.00, 52.18)	(NE: NE, NE)
p-value[d]			NE
p-value[e]			0.31

c) incl. Q2W dosing

	Placebo (N = 39)	Darbepoetin alfa (N = 87)	Treatment Difference (OR: 95% CI)
Subjects with some Q2W Dosing			
Subjects evaluable[a] - n	25	60	
Low IPSS risk category	12	30	
Intermediate-1 IPSS risk category	13	30	
Non-responders - n (%)	15 (60.0)	40 (66.7)	
Responders[b] - n (%: 95% CI)	10 (40.0: 21.13, 61.33)	20 (33.3: 21.69, 46.69)	(0.75: 0.29, 1.97)
p-value[c]			0.56
Response by baseline IPSS category			
Low IPSS risk category			
Non-responders - n (%)	6 (50.0)	21 (70.0)	
Responders[b] - n (%: 95% CI)	6 (50.0: 21.09, 78.91)	9 (30.0: 14.73, 49.40)	(0.43: 0.11, 1.69)
p-value[d]			0.23
Intermediate-1 IPSS risk			
Non-responders - n (%)	9 (69.2)	19 (63.3)	
Responders[b] - n (%: 95% CI)	4 (30.8: 9.09, 61.43)	11 (36.7: 19.93, 56.14)	(1.30: 0.32, 5.24)
p-value[d]			0.71
p-value[e]			0.56

Five subjects with erythroid response during this period (all originally randomized to darbepoetin) had a baseline serum endogenous erythropoietin level of >100 mU/mL.

CHMP comment

Five subjects with erythroid response during the open label period (all originally randomized to darbepoetin) had a baseline serum endogenous erythropoietin level of >100 mU/mL. The MAH should provide details about dosing frequency and WHO class of these 5 patients.

For subjects with only Q3W dosing the Hazard ratio is >1, with no responders in both groups for int-1 MDS patients. For patients with also Q2W dosing the HR is <1, but not significant overall and in the strata.

This underlines the previous assessment that with the Q3W dosing scheme no benefit as of IWG 2006 response criteria was established and makes the change of the primary endpoint even more questionable.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

E23 Summary of Efficacy for trial 20090160

Title: A multicenter, randomised, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anaemic subjects with low or intermediate-1 risk myelodysplastic syndrome (MDS)		
Study identifier	20090160	
Design	(Ongoing) Phase 3, randomized, double-blind, placebo controlled	
	Duration of main phase:	72 weeks (24-week double-blind treatment period and 48-week, open label, active treatment period) long-term follow-up ongoing
Hypothesis	Superiority (comparison to placebo)	
Treatments groups	Subjects: • low or intermediate-1 risk MDS per IPSS with no previous biologic response modifiers to treat MDS • no previous ESAs • baseline hgb ≤ 10.0 g/dL • had not received ≥ 4 units of RBCs during either of 2 consecutive 8-week periods before randomization or any RBC transfusion within 14 days before randomization • baseline endogenous EPO ≤ 500 mU/mL	Dosing: 500 μg Q3W 500 μg Q2W at or after 31 weeks (during active treatment period) if hgb increase < 1.5 g/dL in absence of RBC transfusion (Q2W = every 2 weeks, Q3W = every 3 weeks, RBC = red blood cell)
	Darbepoetin alfa	<u>24-week double-blind treatment:</u> 98 subjects randomized <u>48-week active treatment period:</u> Both treatment arms received darbepoetin alfa

	Placebo		<u>24-week double-blind treatment:</u> 49 subjects randomized <u>48-week active treatment period:</u> Both treatment arms received darbepoetin alfa
Endpoints and definitions	Primary endpoint	Transfusion	Incidence of RBC transfusions from week 5 to EOTP; Incidence of at least 1 RBC transfusion from week 5 to the end of the 24-week double-blind treatment period (also evaluated from week 1 to the end of the double-blind treatment period)
	Secondary endpoint	erythroid response	IWG erythroid response during the double-blind treatment period; Achieving an initial ≥ 1.5 g/dL increase in hemoglobin from baseline and sustaining an average rise of ≥ 1.5 g/dL in a rolling 56-consecutive day period in the absence of RBC transfusion
	In Germany, the original protocol objectives of the study remained unchanged (ie, IWG erythroid response is the primary objective, and RBC transfusion is a secondary objective)		
Database lock	end-of-treatment-phase (EOTP) visit occurred at week 25 or 3 weeks after the last dose of investigational product in the double-blind treatment period Data cut-off: 07 Oct 2015 end-of-active-treatment-period (EOATP) visit occurred at week 72/73 or 3 weeks after the last dose of darbepoetin alfa Data cut-off: 18th February 2016 long-term risk, follow-up with regard to survival and progression to AML was to occur every 26 weeks (± 4 weeks) after the EOATP visit for a minimum of 3 years from the first dose of investigational product Data cut-off: ongoing		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Transfusion Primary Analysis Set (for the analysis of RBC transfusions) and the Primary Analysis Set (for the analysis of erythroid response) included 146 subjects (97 darbepoetin alfa, 49 placebo)			
Descriptive statistics and estimate variability	Treatment group	Placebo	Darbepoetin alfa	Treatment Difference
	Number of subject	N = 49	N = 97	p-value (Two-sided Chi-square test)
	Week 5 to EOTP (week 24)	29	35	0,008
	Subjects transfused - n (%)	59	36	0,008
	Week 1 to EOTP (week 24)	31	39	<point estimate>
	Subjects transfused - n (%)	63	40	<variability>
Effect estimate per				

comparison	Secondary endpoint: Erythroid response	Comparison groups	Dabepoetin alfa compared to placebo (evaluated during the 24-week double-blind treatment period)
		Superiority of darbepoetin alfa and placebo	Subjects evaluated: DA: 75 PBO: 35 Responders - n (%) DA: 11 (14.7) PBO: 0 (0) Non-Responders –n (%) DA: 64 (85.3) PBO: 35 (100.0) 14.7% of subjects in the darbepoetin alfa arm and no subject in the placebo arm had an IWG 2006 erythroid response
		P-value	0.0016
Notes	This phase 3, randomized, double-blind, placebo-controlled study in anemic subjects with low or intermediate-1 risk MDS, darbepoetin alfa was superior to placebo with regard to the incidence of RBC transfusions during the 24-week double-blind treatment period. Darbepoetin alfa was also superior to placebo with regard to the proportion of subjects achieving IWG 2006 erythroid response.		
Analysis description	**Interim Analysis** Of selected efficacy and safety endpoints during the active treatment period (and the double-blind and active treatment periods combined for a small subset of endpoints) was performed after all subjects had either completed the EOATP (week 72/73, or 3 weeks after the last dose of darbepoetin alfa Q3W or 2 weeks after the last dose of darbepoetin alfa Q2W) or withdrawn from study. As subjects in both treatment arms received darbepoetin alfa during the active treatment period, the ability to determine treatment group effects was limited. Thus, these analyses were considered to be descriptive.		

Analysis performed across trials (pooled analyses and meta-analysis)

The MAH performed some comparison of primary and secondary efficacy results across the phase II and III studies.

The ability to compare RBC transfusion rates between studies is limited by differences in the dosing rules; no dose increases were allowed during the double-blind treatment period in Study 20090160, whereas dose increases were allowed after 6 weeks of treatment in Study 20030207.

Table E24 RBC transfusions compared for studies 20090160 and 20030207

		Placebo (N = 49)	Darbepoetin alfa (N = 97)
Week 5 to EOTP (week 24)			
Subjects transfused - n (%)		29 (59)	35 (36)
Week 1 to EOTP (week 24)			
Subjects transfused - n (%)		31 (63)	39 (40)
	ESA-naive (N = 144)	ESA-treated (N = 62)	All Subjects (N = 206)
Week 5 to EOTP (week 28)			
n[a]	141	57	198
Subjects transfused - n (%)	23 (16)	17 (30)	40 (20)
Week 1 to EOTP (week 28)			
n	144	62	206
Subjects transfused - n (%)	26 (18)	21 (34)	47 (23)

CHMP comment

The comparison of the 36% transfused ESA-naïve patients in the pivotal vs. only 16% in the phase II study underlines that the decision to prohibit dose increases during DBTP until week 25 withheld effective treatment from the patients. The benefit of reduction of transfusions for the ESA-naïve group was hence as low as for the ESA-pretreated patients in the phase II study.

The studies used different definitions of erythroid response (IWG 2006 criteria in Study 20090160 and IWG 2000 criteria in Study 20030207). To allow for better comparison of the results between studies, a post hoc analysis was performed to evaluate the data from Study 20030207 according to the more recent IWG 2006 criteria. Erythroid response rate was evaluated during the 24 week double-blind treatment period in Study 20090160, compared with the longer 52 week treatment period in Study 20030207.

In this analysis, erythroid response was defined as an initial increase in haemoglobin of ≥1.5 g/dL from baseline (in the absence of an RBC transfusion on the day of measurement or in the preceding 28 days) and an average increase in haemoglobin of ≥1.5 g/dL from baseline that was sustained for at least 8 weeks after the initial rise.

Compared with Study 20090160 (14.7% in DBTP), higher percentages of subjects in Study 20030207 had an erythroid response in both the ESA-naive (52%) and ESA-treated (26%) strata (Table E25). The higher erythroid response rate in Study 20030207 may have been a result of the ability to increase dose during the test period.

Table E25 IWG 2006 erythroid response according to IWG 2006

	Placebo (N = 49)	Darbepoetin alfa (N = 97)	
Subjects evaluable[a] - n	35	75	
Responders - n (%)	0 (0.0)	11 (14.7)	
Non-responders - n (%)	35 (100.0)	64 (85.3)	
	ESA-Naive (N = 144) n (%)	ESA-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Erythroid response[a]			
Yes	75 (52)	16 (26)	91 (44)
No	50 (35)	32 (52)	82 (40)
Not eligible	19 (13)	14 (23)	33 (16)

CHMP comment

It is not understood why the MAH compared the 24-week DBTP with the extended 52-week treatment period instead of the 28-week treatment period of study 20030207. This should be performed.

In addition the MAH should evaluate the open-label phase of study 20090160 against the phase II study as for both dose increases to Q2W were allowed.

Further between-study analyses and discussion should be performed for baseline prognostic scores such as IPSS, FAB classification, WHO classification, EPO-level, Hb level, bone marrow blasts.

Even though, the previous comment is supported that sufficiently effective treatment for the ESA-naïve patients was withheld by the design of the pivotal study as regards dose increase recommendations. The response was even lower than for the ESA-pretreated patients.

It is, however, noted that ESA-naïve patients in the phase II study were of IPSS category Low in 65% whereas there were 51% in the pivotal study. Also, mean Hb was 9.7g/dl in the phase II and 9.2g/dl in the pivotal study. Hence, those study patients had slightly better baseline factors.

Clinical studies in special populations

CHMP comment

The studies included elderly patients with a mean age of 72.4 and 75.2 years of age.

Only 15% in the phase II study were not White.

Data for other special populations, e.g. paediatrics, are not available.

Supportive study

Study 20130113

Title	**Single-arm, Companion Study to Myelodysplastic Syndrome (MDS) 20090160 Using Darbepoetin alfa for the Treatment of Anaemic Subjects With Myelodysplastic Syndrome**
Study Code	20130113
EudraCT	2013-000727-13
Design	phase 3b, single-arm, open-label, multicentre
FSI / LSLV	12 June 2014 / N/A, study is ongoing
Data cut-off	17 October 2016
Sites	5 sites in BE

Study 20130113 is an ongoing phase 3b companion study to study 20090160 that is conducted in Belgium. The rationale of this study was to provide required access to IP darbepoetin beyond the end of the active treatment period of study 20090160 for subjects that continue to benefit from darbepoetin treatment and to describe the safety of longer-term use in this patient population. Enrolment into the study is closed.

Subjects enrolled into Study 20130113 could continue treatment with darbepoetin alfa for up to 73 weeks or until lack of response, diagnosis of new malignancy, or progression to AML, whichever occurs first.

Eligible subjects were those who completed the active treatment period of Study 20090160 and had an ongoing clinically relevant erythroid response as assessed by the investigator using current response criteria (ie, IWG 2006 response criteria).

Study Endpoints: The primary endpoint of the study was the subject incidence of treatment-emergent adverse events.

Results:

A total of 9 subjects were enrolled, and 2 of these subjects are still participating in the study. 3 of the subjects were women and 6 were men. Age ranged from 55 to 84 years.

Dosing was carried forward from the preceding study. 1 subject received 2 Q3W doses of darbepoetin, with a cumulative dose of 1000 µg administered. The number of doses administered to the other 8 subjects ranged from 26-37, and the cumulative dose ranged from 9000 µg-18500 µg.

5 subjects received RBC transfusions at Hb concentrations ≤9g/dl.

CHMP comment

According to the CSP of study 20130113 (dated 15.04.2013) it was initially expected that more or less all active sites of the pivotal study, i.e. approx. 50, would continue in the phase 3b study, but only 5 sites in BE participated. The enrolment of only 9 patients into a long-lasting treatment phase is a missed chance to generate clinically relevant efficacy and safety data beyond 73 weeks for darbepoetin in MDS patients. The MAH should comment why this was not performed as planned.

The MAH should also clarify whether the patients with >2 doses were on Q2W or Q3W dosing.

No further or more detailed data relevant for efficacy is available. Overall, the information from the 9

patients of study 20130113 is of no further relevance for the efficacy evaluation, as the numbers are too small to draw any conclusions.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose finding study 20030207

The efficacy and safety of the 500µg darbepoetin Q3W dose in subjects with MDS were evaluated in the phase II, stratified, multicentre, single-arm, open-label study conducted in the US.

Patients with Low or Int-1 risk MDS per IPSS (RA, RARS, RAEB with blast count ≤10%, according to FAB classification) with Hb≤11.0 g/dL were included that were either ESA-naive or ESA-treated (stratification factor). No specifications for baseline RBC transfusion use and baseline endogenous EPO were made.

Inclusion of patients with Hb ≤11.0 g/dL at screening is higher than currently recommended for initiation of treatment for symptomatic anaemia of MDS in European treatment guidelines, which is ≤10.0 g/dL. Due to a lack of specification regarding baseline RBC transfusion status or endogenous epoetin level this study could have recruited patients with high transfusion need or Epo>500mU/ml. This was in contrast to current European treatment recommendations and to the criteria set forth in the pivotal study.

At the time of enrolment into the phase II study, which was conducted between 2004-2006, the old WHO 2001 criteria for classification of MDS subgroups still applied. In addition, treatment standards in general might have been different at this time. This might have resulted in enrolment of patients with a slightly different prognostic profile than in the pivotal study.

The initial dose of 500µg Q3W was aligned to the approved dose for chemotherapy induced anaemia. Overall, a fixed dose, not a weight-based dose was to be used. Results suggest that this dose was too low.

The dose adjustment recommendations applicable after 6 weeks, i.e. increase of frequency to Q2W if needed, controlled the following visit scheme to be 2-weekly or 3-weekly. Also, the end of (extended) treatment period was affected (week 27 or 28; weeks 51 or 52). Therefore, all visit-related procedures such as Hb measures or AE reporting etc. occurred likewise at: Q3W: weeks 4, 7, 10, 13, 16, 19, 22, 25, 28 (9 visits) or Q2W: weeks 4, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 (12 visits), and correspondingly between weeks 31-51/52.

To assess efficacy responses, the IWG 2000 criteria, i.e. major and minor erythroid response, were used. The efficacy analysis used 3 periods: test (weeks 1-13, primary), treatment (weeks 1-27/28), and extended treatment (weeks 1-51/52).

Due to a safety review on ESAs performed by the CHMP in 2007 the target range for titration of Hb changed from 11-12g/dl to 10-12g/dl. It is acknowledged that this study was performed when the titration target Hb of 11-12g/dl was still higher than currently recommended and used in the pivotal study.

Analyses in US-only, open-label, single-arm phase II study 20030207 were descriptive only. This is considered to compromise the final B/R assessment for the ESA-pretreated patients. These are also

intended in the proposed indication but were not included in the confirmatory pivotal EU phase III study.

Main study 20090160

The pivotal study was a randomised double-blind multicentre study in 49 active sites in the EU.

The MAH had sought national and central scientific advice 4 times, at the Rapporteur BfArM and the CHMP during planning and conduct phase of the study. Prior to study start (2006 and 2010) main BfArM requests were to conduct a 4-year long-term follow up, evaluate a 1-year placebo-controlled treatment phase and analyse transfusion reduction as the primary endpoint with clinical relevance, consistent with the EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man, Appendix 4 "*Loss of need for transfusion for a defined period of time (in combination with improved haemoglobin levels)*". At the end of enrolment (2014) BfArM was hesitant to accept Amendment #3 which changed the primary endpoint for Germany. The CHMP advice (2016) was sought about acceptability of the study for an extension of indication application.

In-/Exclusion criteria

The pivotal study enrolled Low-or Int-1 primary MDS patients with RA, RARS, RCMD; MDS-U, del5q, or RAEB-1 according to WHO 2008 classification. Hb-level had to be ≤10g/dl with adequate ferritin and transferrin saturation. Secondary MDS, Int-2 or high-risk MDS and a history of AML were excluded. Patients must not have had high transfusion demand (≥4 units of RBC transfusions within 8 weeks) or received RBC transfusions during the 14 days prior to randomisation. Endogenous EPO levels had to be <500mU/ml. Pre-treatment with ESAs, disease modifiers or cytotoxic chemotherapy was also excluded. Overall, the in- and exclusion criteria of the pivotal study defined an ESA-naïve MDS population which corresponds to the current European guideline recommendations for initiating ESA therapy in MDS patients.

Treatment

Eligible subjects were randomized in a 2:1 ratio via an IVRS to receive darbepoetin alfa 500 µg Q3W or placebo Q3W, stratified by screening IPSS category (low versus intermediate-1).

Dose adjustments in the pivotal study were also operated by the IVRS system based on local lab Hb. At or after week 31, for subjects with a haemoglobin increase of <1.5 g/dL and in the absence of RBC transfusion in the prior 28 days, the dose could be escalated from 500 µg Q3W to 500 µg Q2W. If so, the Q2W frequency was then maintained for the duration of the active treatment period, even if the dose was later reduced. Dose reduction was permitted at any time for exceeding Hb threshold or excessive rate of rise.

Dose increase and reduction requirements of the pivotal study are comparably reflected in proposed SmPC section 4.2. However, the dose increase recommendations were not subject of the blinded randomised treatment phase of the phase III study and hence not confirmed with the primary endpoint. The MAH is requested to justify the suitability of the proposed dose increase recommendations based on the open-label phase only.

It is emphasized from the pivotal study protocol that during the active treatment period after week 31 the visits and herewith the visits' study procedures were performed every 2 weeks for patients on Q2W dosing scheme compared to maintenance of every 3 weeks for patients on Q3W scheme (similar to the phase II study. Especially for collection of adverse events and Hb, as well as other endpoints, this is considered as having undoubtedly introduced bias into efficacy and safety results.

Amendments / Change of primary endpoint

The study required many substantial amendments of the protocol as well as many amendments of the two distinct SAPs. This is considered below standard for a phase III study and casts doubt on a careful and robust planning of the study in spite of the various scientific advices obtained.

The primary endpoint was changed twice (Amendments #3 and #4) after 130 of 147 patients were enrolled. The rationale for Amendment #3 states: "*Following an Amgen study team review of blinded data, the pooled IWG erythroid response rate appears too low for the study to meet its primary objective*".

This amendment #3 was not accepted by the German regulatory authority BfArM, after consultation with the Rapporteur's team and the national scientific advice in Nov 2014.

As a result, the primary endpoint for other countries except Germany (CSP Version 4) was: *"The proportion of subjects with at least 1 RBC transfusion from week 5 to EOTP will be analysed using a Chi-squared test for differences and using the CMH method stratified by the IPSS category (low versus intermediate-1). The analysis will be performed on subjects in the Transfusions from Week 5 to EOTP Primary Analysis Set.*" whereas for Germany (CSP version 2) the primary endpoint remained *"Achieving an IWG erythroid response during the double-blind treatment period. IWG erythroid response for non-transfusion dependent subjects is defined as achieving an initial ≥ 1.5 g/dL increase from baseline in haemoglobin level and sustaining an average rise of ≥ 1.5 g/dL in a rolling 56-consecutive day period in the absence RBC transfusion. IWG erythroid response will be determined based on central laboratory haemoglobin values.*"

ICH-GCP (E6) defines: *"1.40 multicentre Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator."* This requirement does also hold for multinational studies. The study 20090160 is not in line with ICH-GCP (E6) requirements.

The problem of having no unique and clear criterion for deciding when the trial is successful is fully evident when the situation of having two effective primary endpoints is related to different versions of the protocol. The assessment makes use of two relevant guidelines – *Reflection paper on methodological issues in confirmatory issues in confirmatory and clinical trials with adaptive design* and *ICH E9 Statistical Principles for Clinical Trials*.

Although the study of interest has not an adaptive design, the guidance is considered relevant. The sponsor did not use a predefined interim analysis. The growing database of incoming data of the study was used not within a framework of an interim analysis, but to program the tables and figures etc., that would be needed for the primary analysis. The review of the data was therefore not a planned interim analysis. The programmer of the tables realized that the primary endpoint data where not as expected and that it would be unlikely that the primary endpoint could be reached.

From our point of view the data were blinded, but informative. A usual reaction to a lower than anticipated response rate would have been to raise the sample size, but not to change the primary endpoint. From our perception, the accidentally unintended detection that the primary endpoint is very unlikely to be successful speaks for itself that there was enough information on the blinded data to trigger a change request for the protocol to establish more promising primary endpoint. After all, due to the change in the primary endpoint, there is a second chance for the trial to be successful.

We consider this as a major flaw of the study.

As a result, and also because no audit of the pivotal study (as well as the phase II) was performed by the sponsor, the Rapporteur requests the adoption of a GCP inspection of the sponsor to verify the data integrity and reliability of the results of efficacy and safety of study 20090160.

Efficacy data and additional analyses

Dose finding study 20030207

206 subjects were included in the analysis, 144 subjects were ESA-naive and 62 subjects ESA-treated. Demographics were well balanced between the 2 strata. The mean age was 75.2 years. Approximately 10% of subjects had endogenous EPO levels ≥500 mU/mL

Of the 73% patients with prior epoetin, the last QW dose was approximately 52,326 U. This corresponds to ~157,000U per 3 weeks. Calculating the darbepoetin dose from this according to current SmPC recommendations, i.e. to divide by 200, this corresponds to 785µg darbepoetin Q3W. The 27% darbepoetin-pretreated patients had a mean last dose of 232µg on a 2-weekly scheme. This corresponds to 700µg/6 weeks. For ESA-pretreated patients mean time from ESA start to enrolment was 1.7 years. Mean Hb prior to study was 9.6g/dl.

During the study, ESA-naïve patients had an average weekly darbepoetin dose of 151µg (or 2.1µg/kg/week). ESA-pretreated patients had an average weekly darbepoetin dose of 174µg (or 2.3µg/kg/week). For comparison, in the pivotal study of epoetin alpha in naïve and pretreated MDS patients (EPOANE3021), where dose increases were allowed, the weekly mean average dose was 683.1 IU/kg.

13% ESA-naïve and 21% ESA-treated patients were counted as not-eligible for the primary endpoint haemoglobin response.

The primary endpoint of erythroid response after 13 weeks test period was reached both in ESA-treated and ESA-naïve patients. 49% naïve had a major, 22% naïve a minor response. In ESA-pretreated responses were observed at 26% and 18%, respectively.

Of the ESA-pretreated patients 15% (*vs.* 4% naïve) did not receive >4 weeks of treatment, which is comparable to the 15% (*vs.* 3%) who withdrew consent. This could be seen as stopping the study early due to underdosing.

For responses counted as transfusion reduction in ESA-treated patients only 1 of 7 had a >50% reduction in transfusions.

While for ESA-naïve patients FAB classes RA and RARS showed comparable erythroid responses of overall >80%, the ESA-pretreated patients had more responses (55%) in the RA compared to 25% in the RARS class. This result could be anticipated as RA patients are known to better respond to ESAs than RARS patients. Results in RAEB class were better in naïve patients, but numbers were too small to draw valid conclusions.

Especially in the ESA-treated stratum it seems that dose increases after 6 weeks were performed to obtain the target Hb of >11g/dl. In view of the fact that the darbepoetin-pretreated patients had mostly been on a Q2W scheme but still had a Hb of <10g/dl, the starting Q3W dosing of 500µg seems to have not been sufficiently effective; similarly for epoetin-QW-dosed patients in comparison to the pre-study dose.

In contrast, MDS patients in the ESA-naïve stratum showed a steep Hb increase during the first 6 weeks with the 500µg Q3W scheme up to the target Hb concentration of >11g/dl.

Overall the ESA-pretreated patients did not respond as well as the ESA treatment-naïve patients over the complete treatment period for Hb response.

The CSR of study 20030207 states: "*An evaluation of haemoglobin response by dosing schedule indicated that increasing the dosing frequency from Q3W to Q2W resulted in little benefit. Among subjects in the erythropoietin-naïve stratum who achieved a haemoglobin response during the entire study, most subjects (82%) achieved that response without a dose increase.*" No information could, however, be found in the dossier/CSR about necessary dose increases or decreases according to protocol after week 6. The MAH is asked to provide information about the changes from Q3W to Q2W in both strata during the extended treatment period, including the referenced evaluation of response by dosing scheme.

The MAH should discuss possible differences in (early) responses between epoetin and darbepoetin-pretreated patients and whether the proposed fixed (starting)-dose recommendation of 500µg Q3W (e.g., in contrast to a weight-based dosing or a Q2W frequency) has similar benefit in both groups, especially when switching the ESA.

Of the 3 tested HRQOL questionnaires (including EQ-5D and EOHA) only the FACT-F(atigue) showed trends over time. Fatigue is one of the major symptoms of anaemia which impairs QoL in MDS patients and is considered relevant for treatment benefit. For the ESA-naïve patients clinically relevant changes, i.e. 3 points and higher, were seen from week 13 ongoing and only in the Hb responder groups. For the ESA-treated patients a stable clinically relevant increase was only visible in the patients with a major Hb response. In general, standard deviations were high so that no further conclusions can be drawn.

Due to the primary efficacy result in the ESA-naïve stratum of the phase II study 20030207, as well as the safety results, the MAH chose the recommended phase III dose of 500µg Q3W in ESA-naïve patients with low-risk and intermediate-1-risk MDS.

It has, however, to be underlined that the phase II efficacy results were obtained under dose-adjustment possibilities, a point that was obviously not sufficiently considered by the MAH.

Main study 20090160

Baseline characteristics

Overall, baseline demographics were balanced between the arms. About 80-85%% of patients were ≥65 years, ~ 43% ≥75 years. All patients were white and about 55% were male. According to IVRS, IPSS scores were equal for low and int-1 MDS with 92% good karyotype. Mean time since MDS diagnosis to randomisation was 12 months.

Baseline differences for WHO classifications are noted (plc. *vs.* darbepoetin): 26.5 *vs.* 9.3% RA, 8.2 *vs.* 17.5% RARS, 38.8 *vs.* 46.4% RCMD, 20.4 *vs.* 13.4% RAEB-1, 4.1 *vs.* 11.3% del5qMDS. Isolated del5q is known to have the best prognosis, followed be comparable good prognoses of RA and RARS, RAEB has the worst prognosis of the eligible MDS classes. However, the noted differences are considered not having introduced bias between the treatment arms.

Mean Hb at baseline was 9.2g/dl, with 5.5% <8g/dl and 21% between 8-9g/dl. For Hb >9-≤10g/dl an imbalance is noted with 32.7 *vs.* 45.4% (plc. *vs.* darbebpoetin) which could have favoured the darbepoetin arm.

58% received no transfusions in the 16 weeks prior to randomisation. More patients in the placebo arm received 3 and more units RBC in the 16 weeks prior to randomisation (30.6% vs. 20.6%) indicating a higher transfusion need at baseline.

Endogenous Epo levels were low in the study population with mean of 118.6mU/ml and a 3rd quartile of 158mU/ml. Thus, 62% in both arms had levels <100mU/ml. The MAH should give details about number of patients with Epo levels <200mU/ml.

Differences in concomitant medical conditions of about 9-10% are noted for hypertension, myocardial infarction (14.3 vs. 4.1%) and cardiac arrhythmia (11.3 vs. 2.0%, plc. vs. darbepoetin, resp.).

About 22% of patients violated the inclusion or exclusion criteria at enrolment, with 5% more violations in the darbepoetin group. Protocol deviations with regard to the disease under study are considered balanced between the arms and have not favoured one or the other group.

Overall, it is considered that the enrolled study patients of the pivotal study reflect an ESA-naïve low/Int-1-risk MDS patient population sufficiently well. However, the MAH's intended indication is only in part reflected by the phase III study population, as no ESA-pretreated patients were included. Thus, a B/R assessment based on confirmatory data can only be performed for these ESA-naïve patients, whereas a B/R evaluation for ESA-pretreated patients with hence more refractory anaemia needs to be based on the only descriptive results of the phase II US study 20030207.

Efficacy results

As the primary endpoint, the incidence of RBC transfusion from week 5 to the end of the double-blind treatment period was statistically significantly lower in the darbepoetin alfa group (36.1%) than in the placebo group (59.2%), p = 0.008.

Interpretation need to take into account, that randomisation was not stratified for the degree of transfusion need and apparently more patients with a higher transfusion need were randomised to the placebo arm.

Notably, in the Per Protocol Set and the category IPSS-Low no significant efficacy was established with regard to transfusion reduction for darbepoetin against placebo; neither so for patients with Hb <8g/dl, as 3/3 and 4/5 needed transfusions, though this is based on small numbers.

No detailed transfusion results could be found for the primary analysis splitted for endogenous serum baseline epo levels or WHO classes. This should be provided. For endogenous epo, an additional subgroup analysis for epo levels <200/≥200mU/ml is requested for RBC transfusions. Neither results could be found about time to first RBC or TT first RBC after week 5.

For the secondary endpoint IWG 2006 Erythroid Response in the Double-blind Treatment Period (= German primary EP) only 75 of 97 (darbepoetin) and 35 of 49 (placebo) patients were evaluable because patients without central baseline Hb values were counted as "not evaluable". It is stated in the study protocol that at each visit a local Hb lab should have been performed in addition to complete blood count including Hb by the central lab, which might have mislead the investigators. The MAH should provide a sensitivity analysis utilising local baseline Hb values for the missing patients, as available.

For "both primary analyses" the exclusion of patients is quite pronounced. No sensitivity analysis has been provided for a conservative approach of imputation of missing values.

The proportion of (evaluated) subjects achieving an IWG 2006 erythroid response during the double-blind treatment period was statistically significantly greater in the darbepoetin alfa group (14.7%) than in the placebo group (0%), p = 0.016. All patients with (evaluated) erythroid response (11 of in total 97 treated with darbepoetin) were in the group of <100mU/ml endogenous EPO. Therefore, safety should also be analysed for these subgroups. In addition, as after a "conservative approach of imputation of missing values" and/or including the a.m. local labs' Hb additional responders with

endogenous Epo of <200mU/ml may become evident, safety results should in addition be subdivided by <200/≥200 mU/ml.

Details of erythroid response according to baseline Hb-subgroups and WHO classification should also be submitted and discussed, as these represent important prognostic factors. Also time to response and duration of response should be evaluated.

The small number of ESA-naïve erythroid responders (14.7%) in the pivotal phase III suggests that the fixed dose of 500µg darbepoetin Q3W SC during the DBTP was too low. Percentages of responders were much lower than in earlier studies (e.g., study 20030207 40% -the basis for the primary sample size calculation-, or those studies summarized in the pivotal CSP Appendix F) and in a comparable study population with epoetin alpha (27%) which led to approval of an MDS indication earlier this year. The applicant is asked to discuss reasons for these obvious differences in responses in view of the proposed dosing recommendations.

No clinically relevant changes to baseline were observed in HQRL scales FACIT overall, FACIT-F or EQ5D in the full (FACIT-Fatigue) analysis set during the DBTP. At least, a clinically meaningful improvement in FACIT-F scores (>6) was observed in "erythroid "responders (here Hb change ≥1g/dl) at week 25, though observed in small subgroups (n=7 and n=11) only. This is in agreement with the results from the phase II study and also with results from a published randomized phase III study with epoetin in lower-risk MDS patients where improvements in QoL were also limited to patients with an erythroid response (Greenberg et al. 2009).

In view of QoL improvement being one of the two main treatment goals that provides clinical benefit in lower-risk MDS patients, as discussed e.g. in the ESMO clinical practice guidelines in 2014, darbepoetin has not shown efficacy with the tested Q3W 500µg dose in erythroid non-responders in the DBTP.

Open-label phase

126 subjects originally randomized to darbepoetin alfa (n = 87 of 98) or placebo (n = 39 of 48) entered the active treatment period of the study. In the open label phase 79% of the darbepoetin patients and 82% of the placebo patients increased their doses from Q3W to Q2W dosing scheme. For the darbepoetin group this is another important demonstration of a too low dosing during the blinded phase up to the primary endpoint.

During the active treatment period, patients who remained with Q3W dosing had an average darbepoetin dose of 143µg/week (ex-plc) or 131µg/week (ex-darb), which corresponds to weight-based 2.1µg/kg/week or 1.7µg/kg/week, respectively.

Patients who increased doses to Q2W had an average dose of 204µg/week (both groups), corresponding to 2.85µg/kg/week (both groups).

Of cause, it is noted that patients who have left the double-blind phase early due to too low dosing could not contribute to this dosing evaluation, which also means that the dose really necessary might still be higher than this.

Patients who remained on the Q3W scheme had more transfusions than those who switched. And for both, the previous placebo and the previous darbepoetin patients, the frequency of transfusions under Q2W dosing was identical with 59%. However, the data presentation from start of treatment until end of open-label phase is considered non-informative. The MAH should provide and discuss data for transfusions and erythroid responses only for the open label phase to be able to compare effects of different dosing regimens.

The following planned analysis was deleted with Amendment#4: "*For the subgroup of subjects who receive a dose escalation to 500 µg Q2W during the active treatment period, summary statistics will be generated for selected haemoglobin, transfusion, and safety endpoints in order to explore the impact of the dose adjustment.*" The MAH should reinitiate to evaluate all the mentioned points, and include time of dose change and further dose adjustments, e.g. due to excessive Hb increase.

Five subjects with erythroid response during the open label period (all originally randomized to darbepoetin) had a baseline serum endogenous erythropoietin level of >100mU/mL. The MAH should provide details about dosing frequency and WHO class of these 5 patients.

For subjects with only Q3W dosing the Hazard ratio is >1, with no erythroid responders in Int-1 MDS patients. For patients with also Q2W dosing the HR is <1, but not significant overall and for either IPSS stratum.

This again underlines the previous assessment that with the Q3W only dosing scheme no benefit as of IWG 2006 response criteria was established and makes the change of the primary endpoint even more questionable.

Although nearly all of the study patients had anti-darbepoetin antibodies at baseline or during the study, no neutralizing antibodies were detected.

Between study comparison

The comparison of the 36% transfused ESA-naïve patients in the pivotal study *vs.* only 16% in the phase II study underlines that the decision to prohibit dose increases during DBTP until week 25 withheld effective treatment from the patients. The benefit of reduction of transfusions for the ESA-naïve group of the pivotal study was hence as low as for the ESA-pretreated patients in the phase II study.

Further between-study analyses and discussion should be performed for baseline prognostic scores such as IPSS, FAB classification, WHO classification, EPO-level, Hb level, bone marrow blasts.

It is, however, noted that ESA-naïve patients in the phase II study were of IPSS category Low in 65% whereas there were 51% in the pivotal study. Also, mean Hb was 9.7g/dl in the phase II and 9.2g/dl in the pivotal study. Hence, the phase II study patients had slightly better baseline factors.

Supportive study 20130113

According to the CSP of study 20130113 (dated 15.04.2013) it was initially expected that more or less all active sites of the pivotal study, i.e. approx. 50, would continue in the phase 3b study, but only 5 sites in BE participated. The enrolment of only 9 patients into a long-lasting treatment phase is a missed chance to generate clinically relevant efficacy and safety data beyond 73 weeks for darbepoetin in MDS patients. The MAH should comment why this was not performed as planned.

No further or more detailed data relevant for efficacy is available. Overall, the information from the 9 patients of study 20130113 is of no further relevance for the efficacy evaluation, as the numbers are too small to draw any conclusions.

Additional expert consultation

A professor in Hematology was contacted by the Co-Rapporteur and he confirmed the beneficial effects of darbepoetin in this indication based on his clinical practice. He stated that in 1/3 of his patients,

haemoglobin increased in patients with low or intermediate-1-risk MDS to such a level that transfusions were no longer needed.

2.4.4. Conclusions on the clinical efficacy

Based on the currently available efficacy data, with the clinical major objections and objections regarding GCP conformity no reliable conclusions can be drawn for the applied extension of indication of darbepoetin in Low/Int-1-risk MDS patients.

From an efficacy point of view the variation is not approvable at the current stage.

A GCP inspection is requested.

2.5. Clinical safety

Introduction

Darbepoetin alfa is a glycoengineered analog of recombinant human erythropoietin (rHuEPO) with 2 extra consensus N-linked carbohydrate addition sites, resulting in a longer mean residence time and a 3-fold longer serum half-life than rHuEPO.

Darbepoetin alfa is approved in the European Union for the treatment of symptomatic anemia associated with chronic renal failure in adults and pediatric patients and in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Based on the cumulative data to date for darbepoetin alfa, the following have been assessed as important identified and potental risks associated with the use of darbepoetin alfa (RMP Version 8.0 17 March 2017, page 21):

Important identified risks

- hypertension, including hypertensive crisis
- thromboembolic events (venous only for nephrology indication)
- convulsions
- allergic reactions (hypersensitivity)
- antibody-mediated PRCA (nephrology indication)
- cerebrovascular disorders (nephrology indication)
- vascular access thrombosis (nephrology indication)

Important potential risks

- ischemic heart disease, including myocardial infarction (nephrology indication)
- cardiac failure (nephrology indication)
- mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer
- antibody-mediated PRCA (oncology indications)

- cerebrovascular disorders (oncology indications)
- acute myeloid leukemia

Based on the safety database review and signal detection from external spontaneous safety databases, a possible causal relationship between the administration of darbepoetin alfa and severe cutaneous reactions, including SJS/TEN and erythema multiforme is assumed. The issue is currently under assessment in an additional type II variation (EMEA/H/C/000332/II/0141).

The current marketing application variation is intended to support the use of darbepoetin alfa for the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndrome.

The safety data for this indication are from the following 3 clinical studies:

• Study 20090160 (146 treated subjects), a phase 3, randomized, double-blind, placebo-controlled study in anemic subjects with low or intermediate-1 risk MDS.

• Study 20030207 (206 treated subjects), a phase 2, single-arm study of darbepoetin alfa in anemic subjects with low or intermediate-1 risk MDS

• Study 20130113 (9 treated subjects), a phase 3b, single-arm, companion study to Study 20090160, which is being conducted to allow continued darbepoetin alfa treatment in subjects who completed the active treatment period of Study 20090160 and had an ongoing clinically relevant erythroid response.

Patient exposure

The safety analysis was based on the integrated data from Studies 20090160 and 20030207 (Safety Analysis Set). For the integration, data from subjects receiving darbepoetin in Study 20090160 were combined with data from all subjects in Study 20030207 (all received darbepoetin alfa). Data from subjects receiving placebo in the double-blind portion of Study 20090160 are presented side-by-side with the darbepoetin alfa data. The data were analysed as summarized below.

Integrated data were analysed separately by Primary Treatment Period and Extended Treatment Period.

The Primary Treatment Period analysis included double-blind data from Study 20090160 (day 1 to week 25) and treatment period data from Study 20030207 (day 1 to week 27/28).

The Extended Treatment Period analysis included active treatment data from Study 20090160 (week 25 to week 72/end of active treatment and the remainder of the extended treatment period data from Study 20030207 (week 27/28 to week 53/end of treatment).

The statistical analyses were performed to characterize the short-term (week 1-25 resp. week 1-27/28) and long-term safety (week 25 resp. week 27/28 till week 53/end of treatment resp. week 72/end of treatment) safety profiles of darbepoetin alfa in subjects with MDS. No formal hypothesis was tested. Descriptive statistics were generated and included number, mean, SD, median, quartile range, minimum, and maximum for continuous variables, and number and percentage for categorical variables.

Analyses were performed on the Safety Analysis Set, which included all subjects who received at least one dose of investigational product. For this analysis of safety, the adverse event data from Study 20030207 were recoded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0, and

adverse events of interest from Study 20030207 were re-identified using standard MedDRA queries.

The following safety endpoints were evaluated in the integrated analysis:

• Exposure to investigational product, including duration of treatment, total number of non-zero doses, dose intensity (average dose per week), cumulative dose, maximum dose received, and most frequently used dose

• Adverse events, including all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, fatal adverse events, adverse events by grade, adverse events of interest

• Laboratory parameters

  - Serum chemistry: alanine amino transferase, aspartate amino transferase, creatinine, and bilirubin
  - Serum erythropoietin
  - Complete blood cell count: eosinophil count, hemoglobin concentration, hematocrit volume, lymphocyte count, monocyte count, platelet count, red blood cell count, and white blood cell count

• Disease progression to AML through the Extended Treatment Period

• Mortality through the Extended Treatment Period

Subgroup analysis:

Subgroup analyses were performed by sex, age group (< 65, ≥ 65, ≥ 75 years), and International Prognostic Scoring System (IPSS). Summary tables were generated by subgroup for all treatment-emergent adverse events, serious adverse events, adverse events by grade, and adverse events of interest.

Long-term safety assessment:

Available safety data from the long-term follow-up period of Study 20090160 and from Study 20130113 were reviewed for disease progression to AML and death. No formal data summaries or analyses were generated due to the limited amount of data.

CHMP comment:

As described by the applicant the submitted safety data of the Phase II study (20030207) and Phase III study (20090160) was pooled. Data from subjects receiving darbepoetin alfa in Study 20090160 were combined with data from all subjects in Study 20030207 (all received darbepoetin alfa). Integrated data were analysed separately for two defined intervals: Primary Treatment Period and Extended Treatment Period.

Due to the following issues the presented integrated safety data need to be interpreted cautious:

° The study population of the Phase II (20030207) included patients that were ESA pre-treated as well as naïve ones. In contrast, in the pivotal study (20090160) ESA pre-treated patients were explicatively excluded due to safety reasons. Currently, the safety analysis in both subgroups (ESA pre-treated and ESA naïve patients cannot be assessed separately. Further analyses are necessary.

° *The strategy to document disease progression to AML was different. In general progression to AML resulted in withdrawal. However in the Phase II study (20030207) progression to AML had to be documented and reported as serious adverse event. In the pivotal Study (20090160) the progression to AML was documented as well but separately, neither as adverse nor as serious adverse event. This leads to uncertainties in the interpretation of progression data.*

° *In both trials a change from a three-weekly dose scheme to a two-weekly dose scheme was allowed. In general this approach can be accepted. However study 20030207 allowed a dose adaption from week six, in study 20090160 dose adjustment was allowed from week 31. In addition the dose adaption resulted in different dosing schemes (2-weekly versus 3-weekly) and thus in different treatment plans (20090160: CSP, Appendix A: Schedule of assessments; 20030207: CSP, Appendix A, Schedule of assessment). Currently the safety of the two dosing subgroups can be assessed separately only for the Extended Treatment Period, while the safety data presented for the Primary Treatment Period include pooled data from both treatment schemes. The safety for the two treatment schemes – 3-weekly, 500 µg Q3W and 2-weekly, 500 µg Q2W - should be presented separately to allow a comparative approach. If and to what extent different visit schedules may have impacted adverse event reporting is uncertain.*

In the integrated analysis, the Primary Treatment Period included 304 subjects who received darbepoetin alfa and 48 subjects who received placebo. Of the subjects who received darbepoetin alfa, 206 (67.8%) participated in Study 20030207, and 98 (32.2%) participated in Study 20090160 (Table S1).

The Extended Treatment Period analysis included 331 subjects who received darbepoetin alfa, including 206 (62.2%) who participated in Study 20030207 and 125 (37.8%) who participated in Study 20090160. Of the 331 subjects assessed in the Extended Treatment Period, 140 received darbepoetin alfa 500 µg in only the Q3W schedule (116 from Study 20030207, 24 from Study 20090160), and 191 subjects received at least 1 dose of darbepoetin alfa 500 µg Q2W (90 from Study 20030207, 101 from Study 20090160) (Table S1). Dose escalation of darbepoetin alfa from 500 µg Q3W to 500 µg Q2W was permitted in the extended treatment period of both protocols based on hemoglobin concentrations.

Table S1: Analysis Set Disposition for Subjects Included in Safety Analyses

	Primary Treatment Period		Extended Treatment Period Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304)	Placebo (N = 48)	Q3W (N = 140)	Q2W (N = 191)	Total (N = 331)
Primary Treatment Period inclusion	304 (100.0)	48 (100.0)	N/A	N/A	N/A
20030207	206 (67.8)	N/A	N/A	N/A	N/A
20090160	98 (32.2)	48 (100.0)	N/A	N/A	N/A
Extended Treatment Period inclusion	N/A	N/A	140 (100.0)	191 (100.0)	331 (100.0)
20030207	N/A	N/A	116 (82.9)	90 (47.1)	206 (62.2)
20090160	N/A	N/A	24 (17.1)	101 (52.9)	125 (37.8)

The median (range) number of doses administered to subjects in the Primary Treatment Period was 8.0 (1 to 13) for subjects receiving darbepoetin alfa and 8.0 (2 to 8) for subjects receiving placebo. The median (range) total number of darbepoetin alfa doses administered once every 3 weeks (Q3W) was 8.0 (1 to 13). The median (range) total number of darbepoetin alfa doses administered once every

2 weeks (Q2W) was 9.0 (1 to 11).

The median (range) duration of dosing was 25.0 weeks (4 to 32) for subjects receiving darbepoetin alfa and 25.0 weeks (7 to 25) for subjects receiving placebo. The average dose of darbepoetin alfa administered per subject ranged from 25.0 to 500.0 µg (median 500.00 µg).

139 subjects (39.1%) in the darbepoetin alfa group and no subject in the placebo group had a dose reduction during the primary treatment period, 105 subjects (34.5%) had 1 dose reduction, 12 (3.9%) had 2 dose reductions, and 2 (0.7%) had 3 dose reductions.

69 subjects (22.7%) in the darbepoetin alfa group and no subject in the placebo group had a dose withheld due to exceeding the protocol-specified hemoglobin threshold of > 12.0 g/dL.

The median (range) number of doses received per subject in the Extended Treatment Period was 11.0 (1 to 23) overall, 7.0 (1 to 17) for subjects receiving only Q3W dosing, and 15.0 (1 to 23) for subjects receiving Q2W dosing. The median (range) total number of Q3W doses administered was 4.0 (1 to 17) overall, 7.0 (1 to 17) for subjects receiving only Q3W dosing, and 3.0 (1 to 15) for subjects receiving Q2W dosing. The median (range) total number of Q2W doses was 12.0 (1 to 20).

The median (range) duration of dosing was 25.0 weeks (3 to 51) overall, 24.0 weeks (4 to 51) for subjects receiving only Q3W dosing, and 42.0 weeks (3 to 51) for subjects receiving Q2W dosing. The median (range) average dose of darbepoetin alfa administered was 482.97 µg (192.9 to 500.0) overall, 325.00 µg (192.9 to 500.0) for subjects receiving Q3W dosing, and 500.00 µg (300.0 to 500.0) for subjects receiving Q2W dosing.

69 subjects (20.8%) had a dose reduction during the extended treatment period, including 18 (12.9%) receiving Q3W dosing and 51 (26.7%) receiving Q2W dosing. Most of these subjects (18.1%) had 1 or 2 doses reduced. Darbepoetin doses were withheld due to exceeding the hemoglobin threshold of > 12.0 g/dL in 86 subjects (26.0%) overall, 46 subjects (32.9%) receiving Q3W dosing, and 40 subjects (20.9%) receiving Q2W dosing.

Table S2: Exposure to investigational Product (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304)	Placebo (N = 48)	Q3W (N = 140)	Q2W (N = 191)	Total (N = 331)
Number of doses received					
n	304	48	111	159	270
Mean	8.3	7.1	7.1	15.1	11.8
SD	3.1	1.9	3.7	6.8	7.0
Median	8.0	8.0	7.0	15.0	11.0
Q1, Q3	7.0, 10.0	8.0, 8.0	5.0, 8.0	11.0, 22.0	6.0, 18.0
Min, Max	1, 13	2, 8	1, 17	1, 23	1, 23
Total Number of Q3W doses of DA received					
n	304	N/A	111	111	222
Mean	6.2	N/A	7.1	4.1	5.6
SD	3.4	N/A	3.7	2.2	3.4
Median	8.0	N/A	7.0	3.0	4.0
Q1, Q3	2.0, 8.0	N/A	5.0, 8.0	3.0, 4.0	3.0, 8.0
Min, Max	1, 13	N/A	1, 17	1, 15	1, 17

CHMP comment:

As already discussed above, the pooled data might be biased due to different study populations and treatment plans in both studies and thus should be regarded with caution.

Since not found in the documentation of the Phase II study (20030207) data regarding dose reduction and dose withheld is requested.

A total of 352 subjects were included in the Primary Treatment Period analysis, including 304 who received darbepoetin alfa and 48 who received placebo. One hundred eighty-three subjects were men (51.0% darbepoetin alfa, 58.3% placebo) and 169 subjects were women (49.0% darbepoetin alfa, 41.7% placebo). Most subjects were white (89.8% darbepoetin alfa, 100% placebo). Median (range) age was 76.0 years (28 to 94) in the darbepoetin alfa group and 72.5 years (52 to 88) in the placebo group.

A low IPSS risk category was reported for 188 subjects (61.8%) receiving darbepoetin alfa and 24 subjects (50.0%) receiving placebo. Intermediate-1 IPSS risk was reported for 106 subjects (34.9%) receiving darbepoetin alfa and 24 subjects (50.0%) receiving placebo. The most common World Health Organization (WHO) classifications of MDS were refractory anemia (RA; 42.1% darbepoetin alfa, 27.1% placebo), refractory anemia with ringed sideroblasts (RARS; 29.6%, 8.3%), refractory cytopenia with multilineage dysplasia (15.1%, 37.5%), and refractory anemia with excess blasts-1 (8.6%, 20.8%).

Of the 331 subjects assessed in the Extended Treatment Period, 167 (50.5%) were men and 164 (49.5%) were women. Most subjects (90.6%) were white. Median (range) age was 75 years (28 to 94). The most common WHO classifications of MDS were RA (42.0%) and RARS (28.1%).

Table S3: Baseline Demographics and Patient Characteristics (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304)	Placebo (N = 48)	Q3W (N = 140)	Q2W (N = 191)	Total (N = 331)
Sex - n (%)					
Male	155 (51.0)	28 (58.3)	65 (46.4)	102 (53.4)	167 (50.5)
Female	149 (49.0)	20 (41.7)	75 (53.6)	89 (46.6)	164 (49.5)
Race - n (%)					
Asian/Japanese/Pacific Islander	7 (2.3)	0 (0.0)	6 (4.3)	1 (0.5)	7 (2.1)
Black	16 (5.3)	0 (0.0)	10 (7.1)	6 (3.1)	16 (4.8)
Hispanic	8 (2.6)	0 (0.0)	4 (2.9)	4 (2.1)	8 (2.4)
White	273 (89.8)	48 (100.0)	120 (85.7)	180 (94.2)	300 (90.6)
Age (years)					
n	304	48	140	191	331
Mean	74.3	72.3	75.9	72.8	74.1
SD	9.7	9.4	9.5	9.7	9.7
Median	76.0	72.5	77.5	74.0	75.0
Q1, Q3	68.0, 81.5	65.5, 80.0	68.0, 83.0	67.0, 80.0	68.0, 81.0
Min, Max	28, 94	52, 88	52, 93	28, 94	28, 94
Age group - n (%)					
18-64 years	50 (16.4)	10 (20.8)	23 (16.4)	33 (17.3)	56 (16.9)
65-74 years	86 (28.3)	17 (35.4)	33 (23.6)	64 (33.5)	97 (29.3)
75-84 years	130 (42.8)	16 (33.3)	57 (40.7)	80 (41.9)	137 (41.4)
≥ 85 years	38 (12.5)	5 (10.4)	27 (19.3)	14 (7.3)	41 (12.4)

Table S4: Baseline Disease Characteristics I (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304)	Placebo (N = 48)	Q3W (N = 140)	Q2W (N = 191)	Total (N = 331)
IPSS risk category (IVRS) - n (%)					
Low	188 (61.8)	24 (50.0)	95 (67.9)	107 (56.0)	202 (61.0)
Intermediate-1	106 (34.9)	24 (50.0)	40 (28.6)	79 (41.4)	119 (36.0)
Missing	10 (3.3)	0 (0.0)	5 (3.6)	5 (2.6)	10 (3.0)
WHO Classification - n (%)					
RA	128 (42.1)	13 (27.1)	77 (55.0)	62 (32.5)	139 (42.0)
RARS	90 (29.6)	4 (8.3)	40 (28.6)	53 (27.7)	93 (28.1)
RCMD	46 (15.1)	18 (37.5)	8 (5.7)	44 (23.0)	52 (15.7)
MDS-U	1 (0.3)	1 (2.1)	0 (0.0)	2 (1.0)	2 (0.6)
MDS with Isolated Del (5q)	11 (3.6)	2 (4.2)	2 (1.4)	11 (5.8)	13 (3.9)
RAEB-1	26 (8.6)	10 (20.8)	12 (8.6)	18 (9.4)	30 (9.1)
RAEB-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	2 (0.7)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.6)

CHMP comment:

The baseline demographics (Table S3) seem to be comparable for both studies.

However the inclusion criteria regarding the MDS classification differed in both studies as in the phase two study the inclusion was carried out following the FAB classification and in the main study following the WHO classification.

As presented in Table S4 (integrated data) a low IPSS risk category was reported for 188 subjects (61.8%) receiving darbepoetin alfa, an Intermediate-1 IPSS risk was reported for 106 subjects (34.9%). A subgroup analysis for IPSS risk category was provided by the applicant (further information see section subgroup analysis).

Adverse events

In the Primary Treatment Period, the subject incidence of treatment-emergent adverse events was 85.5% among subjects receiving darbepoetin alfa and 77.1% among subjects receiving placebo (Table S5).

Serious adverse events were reported in 18.8% of subjects receiving darbepoetin alfa and 16.7% of subjects receiving placebo; fatal adverse events were reported in 2.6% of subjects receiving darbepoetin alfa and 4.2% of subjects receiving placebo. Investigational product was discontinued due to adverse events in 5.9% of subjects receiving darbepoetin alfa and 4.2% of subjects receiving placebo. Similar percentages of subjects in each group reported adverse events of interest (28.3% darbepoetin alfa, 27.1% placebo).

In the Extended Treatment Period, 227 of 331 subjects (68.6%) reported adverse events. The subject incidence of adverse events was 63.6% among subjects receiving darbepoetin alfa only Q3W and 72.3% among subjects receiving darbepoetin alfa Q2W.

Serious adverse events were reported in 15.7% of subjects overall, 12.9% of subjects receiving only Q3W dosing, and 17.8% of subjects receiving Q2W dosing. Discontinuation of investigational product due to adverse events was reported in 5.1% of subjects overall, 5.0% of subjects receiving only Q3W dosing, and 5.2% of subjects receiving Q2W dosing. Fatal adverse events were reported in 2.1% of

subjects overall, 2.9% of subjects receiving only Q3W dosing, and 1.6% of subjects receiving Q2W dosing. Adverse events of interest were reported in 23.6% of subjects overall, 26.4% of subjects receiving only Q3W dosing, and 21.5% of subjects receiving Q2W dosing.

Table S5: Summary of subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
All treatment-emergent adverse events	260 (85.5)	37 (77.1)	89 (63.6)	138 (72.3)	227 (68.6)
Grade ≥ 2	166 (54.6)	23 (47.9)	54 (38.6)	100 (52.4)	154 (46.5)
Grade ≥ 3	66 (21.7)	13 (27.1)	19 (13.6)	47 (24.6)	66 (19.9)
Grade ≥ 4	16 (5.3)	6 (12.5)	7 (5.0)	14 (7.3)	21 (6.3)
Serious adverse events	57 (18.8)	8 (16.7)	18 (12.9)	34 (17.8)	52 (15.7)
Leading to discontinuation of investigational product	18 (5.9)	2 (4.2)	7 (5.0)	10 (5.2)	17 (5.1)
Serious	12 (3.9)	2 (4.2)	6 (4.3)	6 (3.1)	12 (3.6)
Non-Serious	6 (2.0)	0 (0.0)	1 (0.7)	5 (2.6)	6 (1.8)
Fatal adverse events	8 (2.6)	2 (4.2)	4 (2.9)	3 (1.6)	7 (2.1)
Special interest	86 (28.3)	13 (27.1)	37 (26.4)	41 (21.5)	78 (23.6)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Treatment-related treatment-emergent adverse events	22 (7.2)	4 (8.3)	6 (4.3)	8 (4.2)	14 (4.2)
Serious adverse events	2 (0.7)	0 (0.0)	2 (1.4)	1 (0.5)	3 (0.9)
Leading to discontinuation of investigational product	1 (0.3)	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Study 20030207:

Most subjects (92%) had at least 1 adverse event (Table S6). Twenty-one subjects (11% erythropoietin-naïve, 8% erythropoietin-treated) had ≥ 1 adverse event considered by the investigator to be related to treatment. All treatment-related adverse events had an incidence of ≤ 1% of all subjects. Serious adverse events were reported in 62 subjects (30%). Fifteen subjects (6% erythropoietin-naive, 11% erythropoietin-treated) died during the study or within 30 days after the last dose of darbepoetin alfa. None of the deaths were considered related to treatment by the investigator. Twenty-nine subjects (12% erythropoietin-naive, 19% erythropoietin-treated) were withdrawn from study because of adverse events, including the 15 deaths. Fifty-four subjects (24% erythropoietin-naïve, 32% erythropoietin-treated) had at least 1 of these adverse events.

Table S6: Overall summary of adverse events (20030207)

	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Subjects who had any adverse events	134 (93)	55 (89)	189 (92)
Subjects who had treatment-related adverse events	16 (11)	5 (8)	21 (10)
Subjects who had serious adverse events	41 (28)	21 (34)	62 (30)
Subjects who had serious treatment-related adverse events	2 (1)	0 (0)	2 (1)
Subjects who had life-threatening adverse events	7 (5)	3 (5)	10 (5)
Subjects who discontinued from the study because of adverse events	17 (12)	12 (19)	29 (14)
Subjects who died during the study	8 (6)	7 (11)	15 (7)

Study 20090160 (double-blind period):

The subject incidence of all treatment-emergent adverse events was 81.6% in the darbepoetin alfa group and 77.1% in the placebo group. Most adverse events were grade 1 or 2 in intensity (S7). The darbepoetin alfa group had a lower subject incidence of adverse events that were ≥ grade 3 (15.3% vs 27.1%) or ≥ grade 4 (5.1% vs 12.5%) compared with the placebo group. Three subjects (3.1%) in the darbepoetin alfa group and 2 subjects (4.2%) in the placebo group experienced adverse events leading to discontinuation of investigational product during the double-blind treatment period Eleven subjects (11.2%) in the darbepoetin alfa group and 8 subjects (16.7%) in the placebo group experienced serious adverse events during the double-blind treatment period. Three fatal adverse events were reported during the double-blind treatment period. Sixteen subjects (16.3%) in the darbepoetin alfa group and13 subjects (27.1%) in the placebo group experienced an adverse event of interest during the double-blind treatment period

Table S7: Summary of subject Incidence of Treatment–emergent Adverse Events in the double-blind Treatment period (20090160)

	Placebo (N = 48) n (%)	Darbepoetin alfa (N = 98) n (%)	Total (N = 146) n (%)
All treatment-emergent adverse events - n (%)	37 (77.1)	80 (81.6)	117 (80.1)
Grade ≥ 2	23 (47.9)	42 (42.9)	65 (44.5)
Grade ≥ 3	13 (27.1)	15 (15.3)	28 (19.2)
Grade ≥ 4	6 (12.5)	5 (5.1)	11 (7.5)
Serious adverse events	8 (16.7)	11 (11.2)	19 (13.0)
Leading to discontinuation of investigational product	2 (4.2)	3 (3.1)	5 (3.4)
Serious	2 (4.2)	1 (1.0)	3 (2.1)
Non-Serious	0 (0.0)	2 (2.0)	2 (1.4)
Fatal adverse events	2 (4.2)	1 (1.0)	3 (2.1)
Special interest	13 (27.1)	16 (16.3)	29 (19.9)
Treatment-related treatment-emergent adverse events - n (%)	4 (8.3)	5 (5.1)	9 (6.2)
Serious adverse events	0 (0.0)	1 (1.0)	1 (0.7)
Leading to discontinuation of investigational product	0 (0.0)	1 (1.0)	1 (0.7)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)

CHMP comment:

Regarding the incidence of adverse events (Table S5, extended treatment period) the 2-weekly schema (mostly used in the Phase 2 study) seems to be less tolerable than the 3-weekly schema. Thus - as already discussed above - the applicant is asked to submit a post hoc safety analysis which compares the two different schemes that were used (2-weekly vs 3- weekly).

In addition, since not found in the documentation, the applicant is asked to present the severity (Grade 1-5) of the documented adverse events in the Phase II study (20030207).

Common adverse events

The most frequently reported adverse events (i.e., those reported in ≥ 10% of subjects receiving either darbepoetin alfa or placebo) during the Primary Treatment Period were fatigue (25.3% darbepoetin alfa, 8.3% placebo), asthenia (10.9%, 10.4%), and dyspnea exertional (4.6%, 10.4%). Adverse events that occurred with a ≥ 5% higher subject incidence in those receiving darbepoetin alfa compared with placebo were fatigue (25.3% darbepoetin alfa, 8.3% placebo) and pyrexia (7.6%, 2.1%). In most subjects (45 of 77, 58.4%), fatigue was grade 1 in severity (Table S8).

The applicant states that the reason for the imbalance in subject incidence of fatigue between treatment groups is unknown; however, imbalances in baseline characteristics may have contributed. An imbalance in fatigue was also observed in the primary analysis of adverse events in Study 20090160 (17.3% darbepoetin alfa, 8.3% placebo). However, patient assessment of fatigue on the Functional Assessment of Chronic Illness Therapy- Fatigue scale showed a mean (SD) increase (ie, improvement) of 1.1 (8.8) points in the darbepoetin alfa group and a decrease of 0.5 (7.1) points in the placebo group.

The most frequently affected system organ class (SOC) of adverse events was general disorders and administration site conditions (48.0% darbepoetin alfa, 29.2% placebo), which includes the preferred terms of fatigue, asthenia, peripheral edema (7.6% darbepoetin alfa, 8.3% placebo), and pyrexia (ISS Table 14-6.2.1). The second most frequently affected system organ class was musculoskeletal and connective tissue disorders (33.6% darbepoetin alfa, 25.0% placebo). Preferred terms in this system organ class with ≥ 5% subject incidence in either treatment group were arthralgia (8.6% darbepoetin alfa, 6.3% placebo), back pain (8.2%, 4.2%), pain in extremity (6.6%, 4.2%), and musculoskeletal pain (1.6%, 6.3%)

Among subjects receiving darbepoetin alfa in the Extended Treatment Period, the most frequently reported adverse event was fatigue (10.9%); no other adverse events were reported in ≥ 10% of subjects overall. The subject incidence of adverse event preferred terms was similar between those receiving darbepoetin alfa only Q3W and those receiving darbepoetin alfa Q2W; weight decreased (7.1% Q3W, 2.1% Q2W) and asthenia (1.4% Q3W, 8.9% Q2W) were the only adverse events that differed by ≥ 5% between the 2 groups. Most adverse events were grade 1 or grade 2 in severity. Adverse events that were ≥ grade 3 in severity were reported in 19.9% of subjects overall, 13.6% of subjects receiving darbepoetin alfa only Q3W, and 24.6% of subjects receiving darbepoetin alfa Q2W. Adverse events that were ≥ grade 4 in severity were reported in 6.3% of subjects overall, 5.0% of subjects receiving darbepoetin alfa only Q3W, and 7.3% of subjects receiving darbepoetin alfa Q2W. Anemia (2.4% overall, 2.1% Q3W, 2.6% Q2W) was the only ≥ grade 3 adverse event reported in ≥ 2% of subjects overall. No adverse event of Grade 3 or higher severity was reported with ≥ 5% difference between the Q3W and Q2W dose groups.

As in the Primary Treatment Period, the most affected system organ class in the Extended Treatment Period was general disorders and administration site conditions (29.6%). The second most affected system organ class was infections and infestations (25.4%).

Table S8: Adverse Events That Occurred in ≥ 5% of Subjects by Preferred Term (Safety Analysis set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
Preferred Term	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Number of subjects reporting treatment-emergent adverse events	260 (85.5)	37 (77.1)	89 (63.6)	138 (72.3)	227 (68.6)
Fatigue	77 (25.3)	4 (8.3)	13 (9.3)	23 (12.0)	36 (10.9)
Asthenia	33 (10.9)	5 (10.4)	2 (1.4)	17 (8.9)	19 (5.7)
Dizziness	30 (9.9)	3 (6.3)	5 (3.6)	12 (6.3)	17 (5.1)
Arthralgia	26 (8.6)	3 (6.3)	8 (5.7)	10 (5.2)	18 (5.4)
Dyspnoea	26 (8.6)	2 (4.2)	5 (3.6)	15 (7.9)	20 (6.0)
Back pain	25 (8.2)	2 (4.2)	9 (6.4)	11 (5.8)	20 (6.0)
Oedema peripheral	23 (7.6)	4 (8.3)	12 (8.6)	8 (4.2)	20 (6.0)
Pyrexia	23 (7.6)	1 (2.1)	3 (2.1)	10 (5.2)	13 (3.9)
Diarrhoea	20 (6.6)	1 (2.1)	5 (3.6)	9 (4.7)	14 (4.2)
Headache	20 (6.6)	1 (2.1)	5 (3.6)	8 (4.2)	13 (3.9)
Pain in extremity	20 (6.6)	2 (4.2)	2 (1.4)	8 (4.2)	10 (3.0)
Cough	19 (6.3)	2 (4.2)	4 (2.9)	12 (6.3)	16 (4.8)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
Preferred Term	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Dyspnoea exertional	14 (4.6)	5 (10.4)	1 (0.7)	5 (2.6)	6 (1.8)
Nasopharyngitis	11 (3.6)	3 (6.3)	4 (2.9)	11 (5.8)	15 (4.5)
Insomnia	8 (2.6)	3 (6.3)	5 (3.6)	5 (2.6)	10 (3.0)
Musculoskeletal pain	5 (1.6)	3 (6.3)	1 (0.7)	7 (3.7)	8 (2.4)

Study 20030207:

Most subjects (93% Erythropoietin-naïve, 89% Erythropoietin-treated, 92% All subjects) had at least 1 adverse event. The 3 most common adverse events were fatigue (33% erythropoietin-naïve, 47% erythropoietin-treated), peripheral edema (19%, 16%), and dyspnea (16%, 18%). Adverse events that occurred in ≥ 10% of the subjects are listed in Table S9. Twenty-one subjects (11% erythropoietin-naïve, 8% erythropoietin-treated) had ≥ 1 adverse event considered by the investigator to be related to treatment (Table S10). All treatment-related adverse events had an incidence of ≤ 1% of all subjects.

Table S9: Adverse Events That Occurred in ≥ 10 % of Subjects by Preferred Term (20030207)

Preferred Term	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Fatigue	48 (33)	29 (47)	77 (37)
Oedema peripheral	27 (19)	10 (16)	37 (18)
Dyspnoea	23 (16)	11 (18)	34 (17)
Dizziness	27 (19)	6 (10)	33 (16)
Arthralgia	19 (13)	10 (16)	29 (14)
Back pain	17 (12)	9 (15)	26 (13)
Asthenia	17 (12)	8 (13)	25 (12)
Cough	18 (13)	6 (10)	24 (12)
Diarrhoea	15 (10)	7 (11)	22 (11)
Pain in extremity	18 (13)	3 (5)	21 (10)
Anaemia	10 (7)	10 (16)	20 (10)
Pyrexia	11 (8)	7 (11)	18 (9)
Upper respiratory tract infection	6 (4)	9 (15)	15 (7)

Table S10: Treatment-related Adverse Events by System Organ Class and Preferred Term (20030207)

System Organ Class Preferred Term	Erythropoietin-Naïve (N = 144) n (%)	Erythropoietin-Treated (N = 62) n (%)	All Subjects (N = 206) n (%)
Subjects who had treatment-related adverse events	16 (11)	5 (8)	21 (10)
Musculoskeletal and connective tissue disorders	6 (4)	1 (2)	7 (3)
Arthralgia	1 (1)	1 (2)	2 (1)
Bone pain	2 (1)	0 (0)	2 (1)
Flank pain	1 (1)	0 (0)	1 (<1)
Myalgia	1 (1)	0 (0)	1 (<1)
Neck pain	1 (1)	0 (0)	1 (<1)
Pain in extremity	1 (1)	0 (0)	1 (<1)
Shoulder pain	1 (1)	0 (0)	1 (<1)
General disorders and administration site conditions	5 (3)	1 (2)	6 (3)
Injection site pain	2 (1)	0 (0)	2 (1)
Oedema peripheral	1 (1)	1 (2)	2 (1)
Chills	1 (1)	0 (0)	1 (<1)
Injection site reaction	1 (1)	0 (0)	1 (<1)
Skin and subcutaneous tissue disorders	3 (2)	2 (3)	5 (2)
Pruritus	2 (1)	0 (0)	2 (1)
Rash	1 (1)	1 (2)	2 (1)
Rash erythematous	0 (0)	1 (2)	1 (<1)
Nervous system disorders	3 (2)	1 (2)	4 (2)
Headache	1 (1)	1 (2)	2 (1)
Dizziness	1 (1)	0 (0)	1 (<1)
Transient ischaemic attack	1 (1)	0 (0)	1 (<1)
Gastrointestinal disorders	3 (2)	0 (0)	3 (1)
Diarrhoea	2 (1)	0 (0)	2 (1)
Nausea	1 (1)	0 (0)	1 (<1)
Eye disorders	0 (0)	1 (2)	1 (<1)
Conjunctival haemorrhage	0 (0)	1 (2)	1 (<1)
Vascular disorders	1 (1)	0 (0)	1 (<1)
Hypertension	1 (1)	0 (0)	1 (<1)

Study 20090160:

Adverse events occurring in at least 5% of subjects overall are provided in Table S11. The most frequently reported adverse events in the double-blind period (i.e., those occurring in ≥ 10% of subjects in either treatment group) were fatigue (17.3% darbepoetin alfa, 8.3% placebo), asthenia (12.2% darbepoetin alfa, 10.4% placebo), and dyspnea exertional (6.1% darbepoetin alfa, 10.4% placebo). Most adverse events were grade 1 or 2. The darbepoetin alfa group had a lower subject incidence of adverse events that were ≥ grade 3 (15.3% vs 27.1%) or ≥ grade 4 (5.1% vs 12.5%) compared with the placebo group. The most frequently reported ≥ grade 3 adverse events in the darbepoetin alfa group were anaemia (3 subjects) and pneumonia (2 subjects); all other ≥ grade 3 adverse and ≥ grade 4 adverse events were reported in 1 subject each. In the placebo group, the most frequently reported ≥ grade 3 adverse events were asthenia and renal failure (2 subjects each); all other ≥ grade 3 and ≥ grade 4 adverse events were reported in 1 subject each.

Table 11: Adverse Events That Occurred in ≥ 10% of Subjects by Preferred Term in the Double-blind Treatment Period (200090160)

Preferred Term	Placebo (N = 48) n (%)	Darbepoetin alfa (N = 98) n (%)	Total (N = 146) n (%)
Number of subjects reporting treatment-emergent adverse events	37 (77.1)	80 (81.6)	117 (80.1)
Fatigue	4 (8.3)	17 (17.3)	21 (14.4)
Asthenia	5 (10.4)	12 (12.2)	17 (11.6)
Dyspnoea exertional	5 (10.4)	6 (6.1)	11 (7.5)
Nasopharyngitis	3 (6.3)	8 (8.2)	11 (7.5)
Back pain	2 (4.2)	8 (8.2)	10 (6.8)
Pyrexia	1 (2.1)	9 (9.2)	10 (6.8)
Arthralgia	3 (6.3)	6 (6.1)	9 (6.2)
Dizziness	3 (6.3)	5 (5.1)	8 (5.5)
Headache	1 (2.1)	7 (7.1)	8 (5.5)
Dyspnoea	2 (4.2)	5 (5.1)	7 (4.8)
Oedema peripheral	4 (8.3)	3 (3.1)	7 (4.8)

CHMP comment:

In the Primary Treatment period the most frequently affected system organ class (SOC) of adverse events was general disorders and administration site conditions (48.0% darbepoetin alfa, 29.2% placebo). The second most frequently affected system organ class was musculoskeletal and connective tissue disorders (33.6% darbepoetin alfa, 25.0% placebo)

The most affected system organ class in the Extended Treatment Period was general disorders and administration site conditions (29.6%). The second most affected system organ class was infections and infestations (25.4%).

Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set) from Table 14-6.2.1. (Integrated Summary of Safety)

System Organ Class Preferred Term	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Number of subjects reporting treatment-emergent adverse events	260 (85.5)	37 (77.1)	89 (63.6)	138 (72.3)	227 (68.6)
General disorders and administration site conditions	146 (48.0)	14 (29.2)	35 (25.0)	63 (33.0)	98 (29.6)
Musculoskeletal and connective tissue disorders	102 (33.6)	12 (25.0)	25 (17.9)	48 (25.1)	73 (22.1)
Infections and infestations	88 (28.9)	14 (29.2)	30 (21.4)	54 (28.3)	84 (25.4)

Regarding the pivotal study (20090160) as well as the integrated analysis, a discussion of AEs in respect to consideration of causal relationship was not found. The applicant is asked to present and discuss the Treatment-related Adverse Events by System Organ Class and Preferred Term.

The most frequently reported adverse event was fatigue. As fatigue is one of the major symptoms of anaemia respectively of MDS the reported AEs might be due to a change of severity. Imbalances in subject incidence of fatigue might be due to different baseline characteristics. As discussed in in section 2.4 (clinical efficacy) a clinically meaningful improvement in FACIT-F scores (>6) – and thus an improvement in QoL - was limited to patients with an erythroid response.

Adverse events of special interest

Hypertension (incl. hypertensive crisis), thromboembolic events, convulsions, allergic reactions (hypersensitivity), antibody-mediated pure red cell aplasia, cerebrovascular disorders, transient ischemic attacks and heart failure and tumour progression (including mortality) are known identified / potential risk for the approved indications (RMP Version 8.0, 17 March 2017, pages 178ff)

Eighty-six subjects (28.3%) receiving darbepoetin alfa and 13 subjects (27.1%) receiving placebo had an adverse event of interest during the Primary Treatment Period (Table S12). The most frequently reported (ie, ≥ 10% subject incidence) adverse event of interest categories were hypersensitivity (15.1% darbepoetin alfa, 12.5% placebo) and cardiac failure (11.5% darbepoetin alfa, 10.4% placebo). Hypersensitivity consisted primarily of the preferred terms of pruritus (4.3% darbepoetin alfa, 2.1% placebo), rash (3.9%, 2.1%), asthma (1.3%, 0.0%), multiple allergies (1.3%, 0.0%), and wheezing (1.3%, 0.0%). Cardiac failure consisted primarily of the preferred term peripheral edema (7.6% darbepoetin alfa, 8.3% placebo). Hypertension and malignancy categories were both reported in 8 subjects (2.6%) receiving darbepoetin alfa and 2 subjects (4.2%) receiving placebo. Other categories reported in > 1 subject receiving darbepoetin alfa were embolic and thrombotic events (1.3% darbepoetin alfa, 0.0% placebo), central nervous system vascular disorders (1.0%, 2.1%), ischemic heart disease (1.0%, 2.1%), and arterial thromboembolic events (0.7%, 0.0%).

Adverse events of interest were reported in 78 subjects (23.6%) receiving darbepoetin alfa during the Extended Treatment Period, including 37 (26.4%) who received darbepoetin alfa only Q3W and 41 (21.5%) who received darbepoetin alfa Q2W (Table 12). The most frequently reported adverse event of interest category was hypersensitivity (11.2% overall), which consisted primarily of rash (2.1%), conjunctivitis (1.8%), erythema (1.2%), multiple allergies (0.9%), and pruritus (0.9%). Other hypersensitivity events that were reported in > 1 subject were asthma, hypersensitivity, respiratory failure, stomatitis, and urticaria (2 subjects, 0.6% each). Cardiac failure was reported in 30 subjects overall (9.1%). The most frequently reported preferred term in this category was peripheral edema (6.0%). Embolic and thrombotic events were reported in 10 subjects overall (3.0%). The most frequently reported preferred term in this category was transient ischemic attack (1.2%). Malignancies

were reported is 9 subjects overall (2.7%). Other adverse event of interest categories reported in ≥ 1% of subjects overall were hypertension (1.8%), central nervous system vascular disorders (2.4%), ischemic heart disease (1.2%), and arterial thromboembolic events (1.8%).

Table S12: Adverse Events of Interest by Adverse Event Category (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Number of subjects reporting treatment-emergent adverse events	86 (28.3)	13 (27.1)	37 (26.4)	41 (21.5)	78 (23.6)
Hypersensitivity	46 (15.1)	6 (12.5)	17 (12.1)	20 (10.5)	37 (11.2)
Cardiac failure	35 (11.5)	5 (10.4)	15 (10.7)	15 (7.9)	30 (9.1)
Hypertension	8 (2.6)	2 (4.2)	5 (3.6)	1 (0.5)	6 (1.8)
Malignancies	8 (2.6)	2 (4.2)	4 (2.9)	5 (2.6)	9 (2.7)
Embolic and thrombotic events	4 (1.3)	0 (0.0)	5 (3.6)	5 (2.6)	10 (3.0)
Central nervous system vascular disorders	3 (1.0)	1 (2.1)	4 (2.9)	4 (2.1)	8 (2.4)
Ischaemic heart disease	3 (1.0)	1 (2.1)	1 (0.7)	3 (1.6)	4 (1.2)
Arterial thromboembolic events	2 (0.7)	0 (0.0)	3 (2.1)	3 (1.6)	6 (1.8)
Convulsions	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	1 (0.3)	0 (0.0)	2 (1.4)	1 (0.5)	3 (0.9)
Venous thromboembolic events	1 (0.3)	0 (0.0)	1 (0.7)	2 (1.0)	3 (0.9)
Lack of efficacy/effect	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)

Study 20030207:

Fifty-four subjects (24% erythropoietin-naïve, 32% erythropoietin-treated) had at least 1 of these adverse events (Table 13). The most common of these adverse events were neoplasms (8% erythropoietin-naïve, 15% erythropoietin-treated) and hypertension (5%, 6%).

Thromboembolic-related adverse events reported during this study were (erythropoietin-naïve, erythropoietin-treated) aortic stenosis (0, 1), coagulopathy (0, 1), retinal artery occlusion (1, 0), and thrombosis (0, 1). The adverse event of aortic stenosis (occurring in the erythropoietin-treated stratum) was serious. Although graded as a known risk none of the thromboembolic-related adverse events were considered by the investigator to be related to treatment.

Table S13: Adverse Events of Historical Interest by Adverse Event Category (20030207)

AE Category	Erythropoietin-naive (N = 144) n (%)	Erythropoietin-treated (N = 62) n (%)
Number of Subjects Reporting Adverse Events of Historical Interest	34 (23.6)	21 (33.9)
Cardiovascular and Thromboembolic Events	18 (12.5)	10 (16.1)
Arrhythmias	5 (3.5)	2 (3.2)
Cerebrovascular Accident	6 (4.2)	1 (1.6)
Congestive Heart Failure	4 (2.8)	2 (3.2)
Myocardial Infarction/Coronary Artery Disorders	3 (2.1)	3 (4.8)
Embolism/Thrombosis	1 (0.7)	3 (4.8)
Seizure	1 (0.7)	0 (0.0)
Hypertension	7 (4.9)	4 (6.5)
Pure Red Cell Aplasia	0 (0.0)	0 (0.0)
Immune System Disorders	1 (0.7)	0 (0.0)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	12 (8.3)	9 (14.5)

Study 20090160:

Sixteen subjects (16.3%) in the darbepoetin alfa group and 13 subjects (27.1%) in the placebo group experienced an adverse event of interest during the double-blind treatment period (Table 14). The most frequently reported adverse event of interest category was hypersensitivity (10.2% darbepoetin alfa, 12.5% placebo), which consisted primarily of mild to moderate pruritus (3.1% darbepoetin alfa, 2.1% placebo) and rash (2.0% darbepoetin alfa, 2.1% placebo) (Table 14-6.6.2). The subject incidence of cardiac failure was 4.1% in the darbepoetin alfa group and 10.4% in the placebo group. The most frequently reported preferred term in this adverse event category was mild to moderate peripheral edema (3.1% darbepoetin alfa, 8.3% placebo). One subject (1.0%) in the darbepoetin alfa group and 2 subjects (4.2%) in the placebo group experienced adverse events of hypertension. Two subjects (1 in each treatment group) had severe hypertension. Solid tumours (any) were reported in 1 subject (1.0%) in the darbepoetin group (adenocarcinoma of the colon) and 2 subjects (4.2%) in the placebo group (basal cell carcinoma and thyroid neoplasm). All other adverse events of interest occurred in only 1 subject each. One subject in the darbepoetin alfa group experienced a grade 4 pulmonary embolism (categorized as both an embolic/thrombotic event and a VTE), which resolved with treatment.

Table S14: Adverse Events of Interest by Adverse Event Category in the Double-blind Treatment Period (20090160)

	Placebo (N = 48) n (%)	Darbepoetin alfa (N = 98) n (%)	Total (N = 146) n (%)
Subjects who had adverse events of interest - n (%)	13 (27.1)	16 (16.3)	29 (19.9)
Hypersensitivity	6 (12.5)	10 (10.2)	16 (11.0)
Cardiac failure	5 (10.4)	4 (4.1)	9 (6.2)
Hypertension	2 (4.2)	1 (1.0)	3 (2.1)
Malignancies	2 (4.2)	1 (1.0)	3 (2.1)
Embolic and thrombotic events	0 (0.0)	1 (1.0)	1 (0.7)
Venous thromboembolic events	0 (0.0)	1 (1.0)	1 (0.7)
Central nervous system vascular disorders	1 (2.1)	0 (0.0)	1 (0.7)
Ischaemic heart disease	1 (2.1)	0 (0.0)	1 (0.7)

CHMP comment:

Hypertension (incl. hypertensive crisis), thromboembolic events, convulsions, allergic reactions (hypersensitivity), antibody-mediated pure red cell aplasia, cerebrovascular disorders, transient ischemic attacks and heart failure and tumour progression (including mortality) are known identified / potential risk for the approved indications (RMP Version 8.0, 17 March 2017, pages 178ff).

As shown in tables S12-14 (Adverse events of special/historical interest) most of these adverse events occur in the treatment of patients with MDS as well. In the pivotal study (20090160) these AEs were documented somewhat more often in the placebo arm compared to the darbepoetin alfa arm.

Since not found in the documentation, a table indicating related AEs of special interest should be provided together with a discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

Further it should be clarified why AEs that constitute pharmacological class effects considered important identified or important potential risks are not included SmPC section 4.8 for MDS, e.g. thromboembolic events.

Regarding the high level group term of thromboembolic events (venous and arterial) the applicant is asked to submit an additional safety analysis for *patients with an Hb <11 mg/dl versus patients with an Hb >11 mg/dl.*

Since in the main study (20090160) the progression to AML was not documented as (serious) adverse event the data presented in the integrated analysis might be biased in this point as well.

Serious adverse event

In the Primary Treatment Period, serious adverse events were reported in 57 subjects (18.8%) receiving darbepoetin alfa and 8 subjects (16.7%) receiving placebo. Serious adverse events reported in ≥ 2% of subjects receiving darbepoetin alfa were pneumonia (2.6% darbepoetin alfa, 4.2% placebo) and anemia (2.3%, 0.0%). Serious adverse events reported in more than a single subject receiving placebo were pneumonia and renal failure (0.0% darbepoetin alfa, 4.2% placebo).

In the Extended Treatment Period, serious adverse events were reported for 52 subjects (15.7%) overall, 18 subjects (12.9%) receiving darbepoetin alfa only Q3W, and 34 subjects (17.8%) receiving darbepoetin alfa Q2W (Table 9). Serious adverse events that were reported in ≥ 1% of subjects overall

were pneumonia (1.5%), anemia (1.5%), and transient ischemic attack (1.2%).

Table S15: Serious Treatment-emergent Adverse Events Occurring in ≥ 1% of Subjects Receiving Darbepoetin Alfa by System Organ Class and Preferred Term (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
System Organ Class Preferred Term	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Number of subjects reporting treatment-emergent adverse events	57 (18.8)	8 (16.7)	18 (12.9)	34 (17.8)	52 (15.7)
Infections and infestations	23 (7.6)	3 (6.3)	5 (3.6)	13 (6.8)	18 (5.4)
Pneumonia	8 (2.6)	2 (4.2)	1 (0.7)	4 (2.1)	5 (1.5)
Sepsis	5 (1.6)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.6)
Blood and lymphatic system disorders	11 (3.6)	2 (4.2)	5 (3.6)	4 (2.1)	9 (2.7)
Anaemia	7 (2.3)	0 (0.0)	4 (2.9)	1 (0.5)	5 (1.5)
Cardiac disorders	9 (3.0)	1 (2.1)	4 (2.9)	5 (2.6)	9 (2.7)
Cardiac failure congestive	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
General disorders and administration site conditions	8 (2.6)	1 (2.1)	3 (2.1)	4 (2.1)	7 (2.1)
Asthenia	3 (1.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	2 (0.7)	1 (2.1)	4 (2.9)	3 (1.6)	7 (2.1)
Transient ischaemic attack	1 (0.3)	0 (0.0)	2 (1.4)	2 (1.0)	4 (1.2)

CHMP comment:

Less than 20% of patients experienced SAEs. The total number of SAEs was not found and should be provided.

Although the frequency of individual SAEs PT was low and only for the PT pneumonia and anaemia a frequency of more than 2% was observed, it appears reasonable to analyse the aggregation within system organ classes. The most frequent SAEs belonged to the system organ class infection (3.4 % - 7.6 % of patients experienced infections). More than 2 % of patients experienced SAEs from the system organ classes blood and lymphatic system disorders, respiratory, thoracic and mediastinal disorders, cardiac disorders, gastrointestinal disorder, general disorders and neoplasms.

Serious Treatment-Emergent Adverse Events by System Organ Class (Safety Analysis Set) from Table 14-6.2.5 (Integrated Summary of Safety)

	Primary Treatment Period		Extended Treatment Period Darbepoetin alfa (combined)		
System Organ Class (selected)	Darbepoetin alfa (combined) (N=...)	Placebo (N=48) n	Q3W (N=140)	Q2W (N=191)	Total (N=331)
Number of subjects reporting treatment-emergent adverse events	57 (18.8)	8 (16.7)	18 (12.9)	34 (17.8)	52 (15.7)
Infections and infestations	23 (7.6)	3 (6.3)	5 (3.6)	13 (6.8)	18 (5.4)
Blood and lymphatic system disorders	11 (3.6)	2 (4.2)	5 (3.6)	4 (2.1)	9 (2.7)
Respiratory, thoracic and mediastinal	11 (3.6)	1 (2.1)	3 (2.1)	4 (2.1)	7 (2.1)
Cardiac disorders	9 (3.0)	1 (2.1)	4 (2.9)	5 (2.6)	9 (2.7)
Gastrointestinal disorders	8 (2.6)	0 (0.0)	4 (2.9)	3 (1.6)	7 (2.1)
General disorders and administration site conditions	8 (2.6)	1 (2.1)	3 (2.1)	4 (2.1)	7 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and	6 (2.0)	0 (0.0)	2 (1.4)	3 (1.6)	5 (1.5)
Vascular disorders	4 (1.3)	1 (2.1)	1 (0.7)	1 (0.5)	2 (0.6)
Metabolism and nutrition disorders	3 (1.0)	0 (0.0)	3 (2.1)	1 (0.5)	4 (1.2)
Hepatobiliary disorders	2 (0.7)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.6)
Nervous system disorders	2 (0.7)	1 (2.1)	4 (2.9)	3 (1.6)	7 (2.1)
Renal and urinary disorders	2 (0.7	2 (4.2)	2 (1.4)	1 (0.5)	3 (0.9)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.6)

In the primary treatment period only for gastrointestinal SAEs a difference in frequency of 2% or more was observed (in the primary treatment period 8 SAEs with darbepoetin versus 0 SAEs in placebo arm, extended treatment period further 7 SAEs). The individual SAEs PT were diarrhoea, dysphagia, GI haemorrhage, peptic ulcer haemorrhage, proctitis hemorrhagic, ileus, pneumoperitoneum, small bowel obstruction, volvulus, dyspepsia and gastric perforation. A discussion of the gastrointestinal SAEs should be provided.

Due to the small absolute numbers interpretation by difference in frequency only is difficult. A discussion of SAEs in respect to consideration of causal relationship was not found. From the narratives it is obvious that known adverse effects of ESAs were observed and considered related by the investigators, e.g. thromboembolic events (BELCT2013018193; BELCT2014002365, study 20090160). From a mechanistic view it is not understood why thromboembolic events are considered as an adverse effect in one indication and not in the other.

Since not found a table indicating related SAEs should be provided together with a resp. discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

Further it should be clarified why SAEs that constitute pharmacological class effects considered important identified or important potential risks are not included in the SmPC section for MDS, e.g. thromboembolic events.

Deaths (treatment period / long-term FU)

In the Primary Treatment Period fatal adverse events were reported in 2.6% of subjects receiving darbepoetin alfa and 4.2% of subjects receiving placebo. No subjects had fatal adverse events that were deemed related to investigational product by the investigator.

Seven subjects (2.1%) receiving darbepoetin alfa in the Extended Treatment Period had fatal adverse events, including 4 subjects (2.9%) receiving darbepoetin alfa Q3W and 3 subjects (1.6%) receiving

darbepoetin alfa Q2W.

The causes of death are presented in the next table (Table S16).

Table S16: Fatal Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
Preferred Term	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Number of subjects reporting treatment-emergent adverse events	8 (2.6)	2 (4.2)	4 (2.9)	3 (1.6)	7 (2.1)
Acute myelomonocytic leukaemia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myelodysplastic syndrome	1 (0.3)[a]	0 (0.0)	1 (0.7)[b]	0 (0.0)	1 (0.3)[b]
Myeloproliferative disorder	1 (0.3)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac arrest	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Proctitis haemorrhagic	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.3)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Septic shock	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory arrest	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)

	Primary Treatment Period		Extended Treatment Period		
			Darbepoetin alfa (combined)		
System Organ Class Preferred Term	Darbepoetin alfa (combined) (N = 304) n (%)	Placebo (N = 48) n (%)	Q3W (N = 140) n (%)	Q2W (N = 191) n (%)	Total (N = 331) n (%)
Ileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Bacterial sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Pneumonitis	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Failure to thrive	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Cerebral haemorrhage	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal epidural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)

In addition to the reported fatal adverse events during study, the total number of deaths during study and long-term follow-up is presented in the documentation:

Study 20090160:

36/146 subjects died from study day 1 through long-term follow-up, including 24 receiving darbepoetin alfa in the double-blind period and 12 receiving placebo in the double-blind period. Two subjects died during active treatment, and 34 subjects (23 darbepoetin alfa-darbepoetin alfa, 11 placebo-darbepoetin alfa) died during long-term follow-up. Death due to progression to AML was documented for 7 subjects (6 of 98 [6.1%] darbepoetin alfa-darbepoetin alfa and 1 of 48 [2.1%] placebo-darbepoetin alfa). The remaining subject deaths were due to adverse events.

Study 20130113

No deaths were reported in the 9 subjects participating in Study 20090106.

Study 20030207

15 subjects (6% erythropoietin-naïve, 11% erythropoietin-treated) died during the study or within 30 days after the last dose of darbepoetin alfa (CSR Table 11-3). Pneumonia was the only fatal adverse event that occurred in more than 1 subject (0 erythropoietin-naïve, 2 erythropoietin-treated). The fatal

adverse events reported during this study were consistent for the subject population and there were no clinically relevant differences between the erythropoietin-naïve and erythropoietin-treated strata. None of the deaths were considered related to treatment by the investigator.

CHMP comment:

The causes of death on study are due to haematological malignancies, infections, bleeding and cardiac disorders, thus consistent with the causes of death in the target population. The relative proportions in the darbepoetin alfa and the placebo group are similar, while the absolute numbers are small.

In study 20090160 7 patients died from disease progression to AML, see next section. From the narratives it appears that none of the deaths was considered related to treatment by the investigator. The MAH should state potential causal relationships.

In study 20030207 4 patients died from haematological malignancies, none of the deaths was considered related to treatment by the investigator.

Progression to Acute Myeloid Leukaemia

Based on the safety assessment of Amgen Global Safetey Database (AGSD) cases and the literature, there is insufficient evidence to indicate a causal association between darbepoetin alfa therapy and progression from MDS to AML. However, due to the low frequency of reports, incomplete medical information, and the variable natural history of the disorder, Amgen cannot rule out the possibility of a causal association between AML and darbepoetin alfa, and therefore, AML is considered an important potential risk.

In the literature, the estimated background rate of progression to AML in patients with low to intermediate-1 MDS after a median follow-up of 12 to 22 months is approximately 10% to 20% (Shukron et al, 2012; Garcia-Manero et al, 2008).

Study 20030207

Progression to AML was not collected as part of Study 20030207. Available information is provided for subjects who discontinued treatment due to disease progression and for subjects who discontinued for reasons other than disease progression but had disease-progression-related adverse events. A total of 8 subjects discontinued investigational product because of disease progression, including 7 who were erythropoietin-naïve and 1 who had previously received erythropoietin (Table S18). Of the 7 erythropoietin-naïve subjects, 3 developed AML, 1 developed acute leukemia, 1 developed high-risk MDS, and the type of progression was unknown in the remaining 2 subjects. The type of progression is unknown for the 1 erythropoietin-treated subject.

Additionally, 2 erythropoietin-naïve subjects and 2 erythropoietin-treated subjects discontinued investigational product for reasons other than disease progression, but had adverse events associated with disease progression. The 2 erythropoietin-naïve subjects had acute leukemia and myeloproliferative disorder, respectively, and the 2 erythropoietin-treated subjects had acute myelomonocytic leukemia and MDS, respectively. All 4 subjects died of these events (Table S19).

Table S18: Subjects discontinuing Treatment due to disease Progression (20030207)

Subject Number	Type of Progression	Onset of Progression	SAE
	Erythropoietin-naïve		
1206001	severe acute myeloid leukemia	29 weeks	Yes
8352001	unknown	17 weeks	No
8613001	high-risk MDS	46 weeks	No
8718001	severe acute leukemia	49 weeks	Yes
8810016	unknown	unknown	No
9343001	life-threatening acute myeloid leukemia	30 weeks	Yes
9609001	moderate acute myeloid leukemia	29 weeks	Yes
	Erythropoietin-treated		
8730001	unknown	27 weeks	No

Table S19: Subjects discontinuing Treatment for reasons other than disease progression (20030207)

Subject Number	Type of Progression	Serious
Erythropoietin-naïve		
8810005	acute leukemia	Yes
9338007	myeloproliferative disorder	Yes
Erythropoietin-treated		
9150001	acute myelomonocytic leukemia	Yes
9614007	MDS	Yes

Study 20090160

In summary, from study day 1 to the end of active treatment period (EOATP), 4 subjects (4.2%) in the darbepoetin-darbepoetin group and 1 subject (2.2%) in the placebo-darbepoetin group had progression to AML. Two subjects had ≥ 20% marrow blast cells, 2 subjects had ≥ 20% peripheral blast cells, and 1 subject had a myeloid tumor. None of the subjects had pathogenomic cytogenetic abnormalities for AML.

A total of 128 subjects participating in Study 20090160 enrolled in the long-term follow-up (LTFU) period of the study; 118 of these subjects enrolled after completing both the double-blind and active treatment periods, and 10 enrolled directly after completing the double-blind period. Of the 128 subjects, 88 received darbepoetin alfa during the double-blind period and 40 received placebo. As of the data cut-off date for this interim analysis (17 October 2016), 5 subjects (3 receiving darbepoetin alfa during double-blind, 2 receiving placebo during double-blind) had progressed to AML during long-term follow-up.

Table S17: Progression to AML from Study Day 1 to EOTP confirmed by central review (Safety Analysis Set)

	Placebo (N = 48)	Darbepoetin alfa (N = 98)	Treatment Difference
Subject status			
Number of subjects	46	95	
Events[a] - n (%)	1 (2.2)	4 (4.2)	
Marrow blasts ≥20%	0 (0.0)	3 (3.2)	
Peripheral blasts ≥20%	1 (2.2)	2 (2.1)	
Myeloid tumor	0 (0.0)	0 (0.0)	
Pathognomic cytogenetic abnormality	0 (0.0)	0 (0.0)	
Censored - n (%)	45 (97.8)	91 (95.8)	

CHMP comment:

Progression to AML is considered as a potential risk by the applicant (SCS, Section 6, page 46ff, RMP, Version 8.0, page 182).

The long-term follow-up period of the main study (20090160) is still ongoing. Thus the so far presented results are regarded as immature and should be updated accordingly. Currently the information on PD to AML is unclear and – possibly due to different reporting requirements in the studies – difficult to survey.

To assess this important issue adequately, the applicant is asked to present further overviews/summaries:

The number of patients who progressed to MDS, AML and non-AML leukemia (Incidence of progression) during the particular treatment periods and in total should be presented in a table:

	Total MDS Progression		Progression to AML		Progression to non AML acute leukemia	
	Placebo	Darbepoetin alfa	Placebo	Darbepoetin alfa	Placebo	Darbepoetin alfa
Safety analysis set						
Double-blind period						
Aktive treatment Period						
Long-term follow-up						
Total						

In addition the following issues should be presented in form of a table

- *Subject Number / Age / Sex*
- *Treatment schema (2-weekly / 3-weekly)*
- *Pre- treatment (ESA pre-treated / ESA naïve)*
- *Change in IPSS risk category*
- *Change in MDS classification*

° *Time on study at progression*

Furthermore - as discussed in the SA with EMA (EMEA/H/SA/3443/1/2016/II) - the applicant is asked to present all data available from MDS registries.

Safety in special populations / subgroup analysis

Adverse events were evaluated by sex, age (< 65, ≥ 65, and ≥ 75 years) and IPSS (low, intermediate-1 risk) categories. In the Primary Treatment Period, a difference between treatment groups was noted in the system organ class of nervous system disorders for subjects with low IPSS risk (22.9% darbepoetin alfa, 8.3% placebo) compared with subjects having intermediate-1 IPSS risk (22.6% darbepoetin alfa, 25.0% placebo) . The higher subject incidence of nervous system disorders among subjects with low IPSS risk receiving darbepoetin alfa was mainly due to dizziness (10.6% darbepoetin alfa, 4.2% placebo), headache (5.3%, 0.0%), and sciatica (2.1%, 0.0%). In the Extended Treatment Period, nervous system disorders were reported in 13.4% of subjects with low IPSS risk and 20.2% of subjects with intermediate-1 IPSS risk.

A greater difference between treatment groups in serious adverse events was observed in the Primary Treatment Period for subjects ≥ 75 years old (22.6% darbepoetin alfa, 19.0% placebo) compared with subjects ≥ 65 years old (19.3% darbepoetin alfa, 18.4% placebo). Among the 60 subjects < 65 years old, 8 (16%) receiving darbepoetin alfa and 1 (10%) receiving placebo had serious adverse events; caution should be used in drawing inferences for the < 65-year-old age group due to the small sample size. In the Extended Treatment Period, serious adverse events were reported for 16.4% of subjects ≥ 65 years old, 14% of subjects ≥ 75 years old, and 12.5% of subjects < 65 years old.

Adverse events of interest were reported more frequently in the Primary Treatment Period among subjects ≥ 65 years old (29.9% darbepoetin alfa, 28.9% placebo) and subjects ≥ 75 years old (31.0% darbepoetin alfa, 33.3% placebo) compared with those < 65 years old (20.0% darbepoetin alfa, 20.0% placebo); however, the subject incidence was balanced between the darbepoetin alfa and placebo groups. In the Extended Treatment Period, adverse events of interest were reported for 16.1% of subjects < 65 years old, 25.1% of subjects ≥ 65 years old, and 25.3% of subjects ≥ 75 years old.

The applicant states that, although some variability in the subject incidence of adverse events was observed between subgroups based on age, sex, and IPSS risk factor, no trend suggested a difference in the overall safety between the darbepoetin alfa group and the placebo group.

CHMP comment:

As already discussed several times (see above), the integrated safety data should be regarded with caution. However it can be accepted that the conducted subgroup analysis (age / sex / IPSS) present no relevant new information.

Laboratory findings

The MAH states that there are no clinically significant differences were observed between treatment groups for any laboratory parameter evaluated in the Primary Treatment Period as well as in the Extended Treatment Period.

CHMP comment:

The applicant states that no clinically significant differences were observed between treatment groups for any laboratory parameter.

Safety related to drug-drug interactions and other interactions

The clinical results obtained so far do not indicate any interaction of darbepoetin alfa with other substances. However, there is potential for an interaction with substances that are highly bound to red blood cells (eg, cyclosporin, tacrolimus). If darbepoetin alfa is given concomitantly with any of these treatments, blood levels of these substances should be monitored and the dosage adjusted as the hemoglobin rises.

CHMP comment:

No new data available.

Discontinuation due to adverse events

Eighteen subjects (5.9%) receiving darbepoetin alfa and 2 subjects (4.2%) receiving placebo discontinued investigational product due to adverse events during the Primary Treatment Period. Anemia (1.0% darbepoetin alfa, 0.0% placebo) was the only adverse event that led to investigational product discontinuation in more than a single subject. In the Extended Treatment Period, 17 subjects (5.1%) overall, 7 subjects (5.0%) receiving only Q3W dosing, and 10 subjects (5.2%) receiving Q2W dosing, discontinued darbepoetin alfa due to adverse events. Adverse events leading to discontinuation in > 1 subject were anemia (3 subjects, 0.9%) and AML (2 subjects, 0.6%).

CHMP comment:

Since in the pivotal study (20090160) – in contrast to the Phase II study (20030207) - progression to AML was not documented as an AE/SAE the presented integrated data in this section is biased as well and need to be interpreted cautiously.

Post marketing experience

Severe cutaneous reactions

Although not prospectively identified as an adverse event of interest for this marketing application variation, an analysis of postmarketing safety data was recently conducted for severe cutaneous reactions, including Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN), based on the receipt of 2 cases of TEN coincident with darbepoetin alfa therapy. Overall, based on the safety database review and signal detection from external spontaneous safety databases, the results suggested a possible causal relationship between the administration of darbepoetin alfa and severe cutaneous reactions, including SJS/TEN and erythema multiforme.

In a post-hoc analysis of data pooled from Studies 20090160 and 20030207, severe cutaneous adverse reaction events were reported in 7 of 304 subjects (2.3% [95% CI: 0.93, 4.69]) receiving darbepoetin alfa and 1 of 48 subjects (2.1% [95% CI: 0.05, 11.07]) receiving placebo during the Primary Treatment Period and 9 of 331 subjects (2.7% [95% CI: 1.25, 5.10]) of subjects receiving darbepoetin alfa during the Extended Treatment Period.

CHMP comment:

Based on the safety database review and signal detection from external spontaneous safety databases, a possible causal relationship between the administration of darbepoetin alfa and severe cutaneous reactions, including SJS/TEN and erythema multiforme is assumed. The issue is currently under assessment in an additional type II variation (EMEA/H/C/000332/II/0141).

2.5.1. Discussion on clinical safety

This variation is intended to support a new indication for darbepoetin alfa, i.e. for the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndrome. The safety data for this indication are from the following 3 clinical studies:

- Study 20090160 (146 treated subjects), a phase 3, randomized, double-blind, placebo-controlled study in anemic subjects with low or intermediate-1 risk MDS. This study investigated in a 24 week double-blind placebo-controlled period the 3-weekly regimen and in the 48 week extension part (active treatment period) continuation with the same dose (3 weekly scheme, 500 µg Q3W) and the dose escalation (2 weekly scheme, 500 µg Q2W) depending on the response.
- Study 20030207 (206 treated subjects), a phase 2, single-arm open-label study of darbepoetin alfa in anemic subjects with low or intermediate-1 risk MDS. In this 52 week study the treatment started with a 3 weekly scheme (500 µg Q3W) and allowed dose escalation from week 6 (500 µg Q2W).
- Study 20130113 (9 treated subjects), a phase 3b, single-arm, companion study to Study 20090160, in subjects who completed the active treatment period of Study 20090160 and had an ongoing clinically relevant erythroid response.

The safety data of these studies were pooled; data from subjects receiving darbepoetin in the pivotal study (20090160) were combined with data from all subjects in Phase II study (20030207) (all received darbepoetin alfa). Integrated data were analysed separately for two defined intervals: Primary Treatment Period and Extended Treatment Period.

The Primary Treatment Period includes data from the double-blind part of Study 20090160 up to week 25 and data up to week 27/28 from Study 20030207. Data from subjects receiving placebo in the double-blind portion of Study 20090160 are presented side-by-side with the darbepoetin alfa data.

The Extended Treatment Period includes the safety data from darbepoetin alfa treatment from Study 20090160 week 25 to 72/resp. end of treatment and from Study 20030207 week 27/28 to 53/resp. end of treatment.

Due to differences in the study design and study populations the presented integrated safety data need to be interpreted cautiously:

- The study population of the Phase II study (20030207) included patients that were ESA pre-treated as well as ESA naïve ones. In contrast, in the pivotal study (20090160) ESA pre-treated patients were explicatively excluded due to safety reasons. Currently the safety in the subgroup of ESA pre-treated patients cannot be assessed separately. Further analyses addressing the safety in ESA pre-treated patients are necessary.

- In both trials a change from a three-weekly dose scheme (500 µg Q3W) to a two-weekly dose

scheme (500 µg Q2W) was allowed. While in general dose titration for ESAs is acceptable, the rules for dose adjustment were different in the studies: Study 20030207 allowed a dose adaption starting from week six, in Study 20090160 dose adjustment was allowed only from week 31. In addition the different dosing schemes (2-weekly versus 3-weekly) resulted in different visit schedules. Currently the safety of the two dosing subgroups can be assessed separately only for the extended treatment period, while in the safety data presented for the Primary Treatment Period include pooled data from both treatment schemes. The safety for the two treatment schemes – 3-weekly, 500 µg Q3W and 2-weekly, 500 µg Q2W -should be presented separately to allow a comparative approach from the start of treatment. If and to what extent different visit schedules may have impacted adverse event reporting is uncertain.

- The strategy to document disease progression to AML was different: In general progression to AML resulted in withdrawal from the studies. However, in the Phase II study 20030207 progressions to AML had to be documented and reported as serious adverse event. In the Phase III study 20090160 the progression to AML was documented as well but separately, neither as adverse nor as serious adverse event. This leads to uncertainties in the interpretation of progression data.
-

The phase II study was performed 2004-2007 and the phase III study 2011-2015. The inclusion criteria regarding the MDS classification differed: in the phase II study the inclusion following the FAB classification and in the pivotal study following the WHO 2008 classification. The long-time interval and the application of different classification systems might have resulted in enrolment of patients with a somewhat different prognosis profile than in the pivotal study. As presented in Table S4 a low IPSS risk category was reported for 188 subjects (61.8%) receiving darbepoetin alfa, an Intermediate-1 IPSS risk was reported for 106 subjects (34.9%).

Apparently the other baseline demographics (Table S3) seem to be comparable for both studies.

The presentation of AEs, SAEs, AEs of special interest indicates SOC and preferred terms. Obviously there are differences in the presentation of the common adverse events between the individual studies. The impact on the integrated analysis is uncertain.

Most frequently reported adverse events (ie, ≥ 10% of subjects receiving either darbepoetin alfa or placebo) during the Primary Treatment Period were fatigue (25.3% darbepoetin alfa, 8.3% placebo), asthenia (10.9%, 10.4%), and dyspnea exertional (4.6%, 10.4%). Adverse events that occurred with a ≥ 5% higher subject incidence in those receiving darbepoetin alfa compared with placebo were fatigue (25.3% darbepoetin alfa, 8.3% placebo) and pyrexia (7.6%, 2.1%). Among subjects receiving darbepoetin alfa in the Extended Treatment Period, the most frequently reported adverse event was fatigue (10.9%); no other adverse events were reported in ≥ 10% of subjects overall. The subject incidence of adverse event preferred terms was similar between those receiving darbepoetin alfa only Q3W and those receiving darbepoetin alfa Q2W; weight decreased (7.1% Q3W, 2.1% Q2W) and asthenia (1.4% Q3W, 8.9% Q2W) were the only adverse events that differed by ≥ 5% between the 2 groups. Since not found in the documentation, the applicant is asked to present grades (Grade 1-5) of the incidences of adverse events in the Phase II clinical trial (20030207).

As fatigue is one of the major symptoms of anaemia resp. of MDS the reported AEs might be due to a change of severity. Imbalances in subject incidence of fatigue might be due to different baseline characteristics. However, a clinically meaningful improvement in FACIT-F scores (>6) – and thus an improvement in QoL - was limited to patients with an erythroid response (section 2.4.).

Imbalance in the subject incidence of fatigue was also observed in the double-blind treatment period in

Study 20090160 (17.3% darbepoetin alfa, 8.3% placebo). The reason for the mentioned imbalance between treatment groups favouring placebo is unknown. This is a surprising finding as one would expect less fatigue in the active treatment group. The Applicant should elaborate on this.

Due to the small absolute numbers of the individual PT interpretation by difference in frequency only is difficult. Hypertension (incl. hypertensive crisis), thromboembolic events, convulsions, allergic reactions (hypersensitivity), antibody-mediated pure red cell aplasia, cerebrovascular disorders, transient ischemic attacks and heart failure and tumour progression (including mortality) are known identified / potential risk for the approved indications (RMP Version 8.0, 17 March 2017, pages 178ff). In study 20090160 these AEs were documented somewhat more often in the placebo arm compared to the darbepoetin alfa arm. Since not found in the documentation, a table indicating related AEs should be provided together with a discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

Regarding the incidence of adverse events in the individual studies the 2-weekly scheme (mostly used in the Phase 2 study) seems to be less tolerable than the 3-weekly schema. More grade 3 and 4 events and more serious adverse events were observed in the Q2W group in the extended treatment period (Table S5). The applicant is asked to submit a post hoc safety analysis which compares the two different schemes (Q2W vs Q3W) as well as the different populations (ESA naïve and ESA pre-treated patients).

Since the responses apparently depend on endogen epoetin levels at baseline, the applicant is asked to present additional safety analysis for patients with low versus high serum epoetin levels.

SAEs were experienced by 12.9 – 18.8% of patients with the highest proportion in the darbepoetin alfa group in the primary treatment period and the Q2W group in the extended treatment period. Since not found the total number of SAEs should be provided.

Although the frequency of individual SAEs PT was low and only for the PT pneumonia and anaemia a frequency of more than 2% was observed, it appears reasonable to analyse the aggregation within system organ classes (SOC). The most frequent SAEs belonged to the SOC infection (3.4 % - 7.6 % of patients experienced infections). More than 2 % of patients experienced SAEs from the SOCs blood and lymphatic system disorders, respiratory, thoracic and mediastinal disorders, cardiac disorders, gastrointestinal disorder, general disorders and neoplasms.

In the primary treatment period only for gastrointestinal SAEs a difference in frequency of 2% or more was observed (in the primary treatment period 8 SAEs with darbepoetin versus 0 SAEs in placebo arm, extended treatment period further 7 SAEs). A discussion of the gastrointestinal SAEs should be provided.

Due to the small absolute numbers interpretation by difference in frequency only is difficult. A discussion of SAEs in respect to consideration of causal relationship was not found. From the narratives it is obvious that known adverse effects of ESAs were observed and considered related by the investigators, e.g. thromboembolic events (BELCT2013018193; BELCT2014002365, study20090160). From a mechanistic view it is not understood why thromboembolic events are considered as an adverse effect in one indication and not in the other. Since not found a table indicating related SAEs should be provided together with a resp. discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

In addition it should be clarified why AE/SAEs that constitute pharmacological class effects considered important identified or important potential risks are not included in SmPC section 4.8 for MDS, e.g. thromboembolic events.

Causes of death on study were reported as haematological malignancies, infections, bleeding and cardiac disorders, thus generally consistent with the causes of death in the target population. The relative proportions in the darbepoetin alfa and the placebo group are similar, while the absolute numbers are small.

In the phase II study (20030207) 4 patients died from haematological malignancies, none of the deaths was considered related to treatment by the investigator. In the pivotal study (20090160) 7 patients died from disease progression to AML. From the narratives it appears that none of the deaths was considered related to treatment by the investigator. The MAH should state potential causal relationships.

Progression to AML is considered as an identified potential risk by the applicant (SCS, Section 6, page 46ff, RMP, Version 8.0, page 178 ff). The long-term follow-up period of the main study (20090160) is still ongoing. Thus the so far presented results are regarded as immature and should be updated. Currently the information on PD to AML is unclear and – possibly due to different reporting requirements in the studies – difficult to survey. The applicant is asked to present the information on MDS progression, progression to AML, progression to non-AML acute leukemia by time/treatment period and treatment arm in a table (see LoQ).

In addition the following issues should be presented in form of a table: Patient (Identifier, Age, Sex; Treatment scheme (2-weekly / 3-weekly); Pre- treatment (ESA pre-treated / ESA naïve); Change in IPSS risk category; Change in MDS classification; time on study at progression.

The applicant is requested to discuss these data. Furthermore, the applicant is asked to present all data available from MDS registries (SA EMA, EMEA/H/SA/3443/1/2016/II).

Available safety data from the long-term follow-up period of Study 20090160 and from Study 20130113 were reviewed only for disease progression to AML and death and no formal data summaries or analyses were generated due to the limited amount of data. Thus there is uncertainty about unfavourable effects on the very long term. However there is a theoretical risk that darbepoetin promotes malignancies. The applicant is asked on which base this risk can be ruled out.

AEs that are considered potential or identified risks in other indications as well as adverse events of special/historical interest that were observed in MDS patients should be included in the SmPC (section 4.8) unless otherwise justified. A statement on potential progression to AML should be included in the SmPC as well (section 4.4).

2.5.2. Conclusions on clinical safety

Based on the currently available safety data no reliable conclusions can be drawn for the applied extension of indication of darbepoetin in Low/Int-1-risk MDS patients.

For a full evaluation of the safety profile several questions need to be addressed and supplementary post hoc safety analyses need to be conducted.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 31.10.2017.

2.6. Risk management plan

2.6.1. Summary of the PRAC Rapporteur's Assessment Report

With the submitted RMP version 8.0 DLP 17 March 2017 the MAH identifies the following safety concerns. The red underlined scripture reflect the changes made by the MAH in the frame of this variation.

Important identified risks	hypertension, including hypertensive crisis thromboembolic events (venous only for nephrology indication) convulsions allergic reactions (hypersensitivity) antibody-mediated PRCA (nephrology indication only) cerebrovascular disorders (nephrology indication only) vascular access thrombosis (nephrology indication only)
Important potential risks	ischemic heart disease, including myocardial infarction (nephrology indication only) cardiac failure (nephrology indication only) mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer antibody-mediated PRCA (oncology and MDS indications only) cerebrovascular disorders (oncology and MDS indications only) acute myeloid leukemia (MDS indication only)
Missing information	risks during pregnancy and lactation ~~pediatric patients~~ hyporesponders ~~safety related to higher doses administered in patients with CRF (nephrology indication only)~~

Having considered the updated data in the safety specification the assessor in principle agrees that the safety concerns listed by the MAH could be appropriate. However, the MAH is asked to provide satisfactory responses to the following issues also outlined in the List of Questions (see below).

Important identified and potential risks

At present it is endorsed for the MDS indication to define PRCA as important potential risk since no adverse events of antibody-mediated PRCA were reported in any MDS study to date. However as it is an identified risk in other indications it should be observed / monitored in MDS as well.

Cerebrovascular disorders are classified as important potential risk in cancer patient. Hence, it is agreed with the MAH also to consider this for the MDS indication.

No adverse events of vascular access thrombosis were reported in any MDS study to date. However as it is an identified risk in other indications it should be observed /monitored in MDS as well. Hence the MAH is asked also at least to include it as important potential risk for MDS.

Events of ischemic heart disease, including myocardial infarction were observed in studies with MDS patients. Hence this safety concern should also be defined for the MDS indication.

Missing information

a) “Safety related to higher doses administered in patients with CRF (nephrology indication only)” has been deleted by the MAH due to finalization of a Meta-analysis for re analysis of clinical trial data concerning hemoglobin levels and ESA doses in CRF patients. Back than addition was requested in 2013 by EMA following CHMP approval of Aranesp® QM dosing.

The objective of this study was as follow.

To analyze the existing study data in order to:

•summarize subject incidence of outcomes of interest including all-cause mortality, cardiovascular events, cerebrovascular events, and the corresponding composite endpoints

•explore the relationship between hemoglobin and outcomes of interest for all subjects, and in subjects on dialysis or not on dialysis

•explore if the relationship between hemoglobin and outcomes of interest varies amongst diabetic and non-diabetic subjects, diabetic and non-diabetic subjects on dialysis, and diabetic and non-diabetic subjects not on dialysis and examine the heterogeneity in subject characteristics at baseline between these different subgroups

•provide evidence to decide about necessitated adjustments of the treatment specifications of ESA in special patient groups; the results of the analyses will be discussed in this context

•explore any ESA dose association with cardiovascular events (all), cardiovascular events (fatal) and cerebrovascular events (all) (independently of hemoglobin level).

The MAH is asked to provide a very short summary about the main outcomes/ conclusions drawn which would help to conclude on whether or not deletion from Missing Information is justified.

b) The MAH took the opportunity also to delete Pediatric patients from the table.

The MAH states that “(…) the safety and efficacy of darbepoetin alfa have not been established in pediatric patients with cancer or MDS (…)”. Hence, both cancer and MDS indications are restricted to adults. In conclusion, it is not overall agreed with the MAH to completely delete “Paediatric patients” from the table. At present no paediatric data have been submitted for the MDS indication. For that reason, for the time being this safety concern should remain in the table for cancer and MDS indication.

In summary, the proposed Routine risk minimisation measures are not considered overall sufficient to minimise the risks of the product in the proposed MDS indication for the following reason:

With regard to the MDS indication the MAH proposed changes to the safety concerns. Moreover, additional requirements were also made by the assessor in this regard. Hence, adverse events identified as important risks for other indications were observed for MDS as well or were at least plausible for this indication and should therefore also be considered in the product information. The risk of progression to AML should also be adequately reflected there.

In conclusion, the RMP could be acceptable provided an updated RMP (in particular to be submitted as both tracked and clean version) and satisfactory responses to the list of outstanding issues is submitted.

2.6.2. Comments from CHMP Rapporteur

Safety

- AEs that are considered important identified or important potential risks for other indications were observed in MDS patients as well but are currently not yet included in the product information. In addition the risk of progression to AML should be adequately reflected.
- AEs that are considered potential or identified risks in other indications as well as adverse events of special/historical interest that were observed in MDS patients should be included in section 4.8, unless otherwise justified. In section 4.4 a statement on potential progression to AML should be included.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.6, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly and commented by Rapporteur as attached.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and commented by Rapporteur QRD as attached.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has not been submitted by the applicant.

CHMP comment

No user testing was performed for the amended PL and no justification is provided. The MAH is asked to submit a respectively completed module 1.3.

3. Benefit-Risk Balance

Overall, the presentation of the clinical data in the dossier (modules 2 and 5) was of improvable quality. This is reflected by the lots of questions about un-provided neglected (and/or previously deleted) efficacy (and safety) data and analyses that are essential for a proper and reliable benefit-risk evaluation in the proposed target population with the proposed dosing.

Benefits

Beneficial effects

As from the pivotal study, the incidence of RBC transfusion from week 5 to EOTP week 25 (during the double-blind treatment period) was statistically significantly lower in the darbepoetin group (36.1%) than in the placebo group (59.2%), p = 0.008.

For Intermediate-1-risk MDS patients the incidence of RBC transfusion was statistically significantly lower in the darbepoetin group (39.6%) than in the placebo group (70.8%) with HR 0.27 (95% CI 0.09, 0.77).

For Low-risk patients the incidence of RBC transfusion was lower in the darbepoetin group (32.7%) than in the placebo group (48.0%), though not statistically significant with HR 0.53 (95% CI 0.20, 1.41).

In the baseline Hb group of >9-≤10g/dl the incidence of RBC transfusion was statistically significantly lower in the darbepoetin group (11.4%) than in the placebo group (37.5%) with HR 0.21 (95% CI 0.05, 0.85). Patients divided for other baseline Hb groups had also less RBC transfusions though of no statistical significance or statistics were not evaluable.

The number of RBC units transfused from week 5 to the EOTP was lower in the darbepoetin arm (2.6 units; 95% CI: 1.8, 3.4) than in the placebo arm (4.1 units; 95% CI: 3.0, 5.3) (p = 0.038).

The proportion of subjects achieving an IWG 2006 erythroid response during the double-blind treatment period was statistically significantly greater in the darbepoetin group (14.7%) than in the placebo group (0%), p = 0.016.

All patients with (evaluated) erythroid response (11 of in total 97 treated with darbepoetin) were in the group of <100mU/ml endogenous EPO.

In the phase II study 49% ESA-naïve had a major and 22% ESA-naïve patients had a minor response according to IWG 2000 criteria. In ESA-pretreated responses were observed at 26% and 18%, respectively.

During the treatment period (weeks 1-27/28), the proportions of subjects who achieved a major erythroid response were 58% and 31% in the ESA-naive and ESA-treated strata, respectively.

While the ESA-naïve patients with WHO-classes RA and RARS showed comparable erythroid responses of overall >80%, the ESA-pretreated patients had more responses (55%) in the RA compared to 25% in the RARS class.

In the test period 17% ESA-naïve patients were transfused and 35% ESA-treated patients were transfused.

Mean changes from baseline in Hb concentrations ranged from 1.1-1.4 g/dL in the ESA-naïve stratum and from 0.3-0.5 g/dL in the ESA-treated stratum.

Uncertainty in the knowledge about the beneficial effects

As regards the pivotal study, due to the data-driven change of the primary endpoint that was based on informative (though blinded) data review at the end of recruitment, the exclusion of a great proportion of patients counted unevaluable and the different visit scheme for Q3W *vs.* Q2W dosed patients in the open-label phase, benefits are currently considered uncertain, because the reliability of the data is questioned.

In addition many further subgroup or sensitivity analyses are currently lacking that are necessary to thoroughly assess benefits, e.g., for WHO 2008 classes, for Hb subgroups, for endogenous serum epoetin levels.

Uncertainty on the strength of the effect on RBC transfusions arises as more patients in the placebo arm received 3 and more units RBC in the 16 weeks prior to randomisation (30.6% vs. 20.6%) indicating a higher transfusion need at baseline.

In the open label phase 79% of the darbepoetin patients and 82% of the placebo patients increased their doses from Q3W to Q2W dosing scheme. From the responses for RBC transfusion incidence in the open-label phase when all patients received darbepoetin it can be derived that the increase of the dosing frequency from Q3W to Q2W resulted in lower numbers of transfused patients.

Even if the possible increases of dose to Q2W frequency has improved transfusion incidence and Hb responses compared to Q3W only, this was only tested in the open-label phase without controlled conditions. As such, the dose adjustment (i.e. increase) recommendations proposed in SmPC section 4.2 are based on this uncontrolled treatment phase only. For subjects with only Q3W dosing the Hazard ratio is >1, with no erythroid responders in Int-1 MDS patients. For patients with also Q2W dosing the HR is <1, but not significant overall and for either IPSS stratum after the open-label phase.

Clinically meaningful improvements of quality of life were not observed during the double-blind period. HRQOL benefits as of increased scores of FACIT-Fatigue were only observed after the open-label phase and only in Hb-responders.

Uncertainties about the benefits from the phase II study are mainly grounded on the fact that this was an open-label, single-arm, US study with descriptive endpoint analyses only. Also here, the visit scheme of Q3W and Q2W was not identical and may have compromised the efficacy results.

Inclusion criteria resulted in a population not fully comparable to MDS patients in the focus of current European treatment guidelines, e.g. regarding endogenous epo levels, baseline Hb, or WHO 2001 classes.

ESA-pretreated patients were only included in this US study but not investigated in the EU so that it is unclear whether the results can be reliably transferred.

Of the ESA-pretreated patients 15% (*vs.* 4% naïve) did not receive >4 weeks of treatment, which is comparable to the 15% (*vs.* 3%) who withdrew consent.

For ESA-pretreated patients who could have had prior epoetin or darbepoetin it is unclear whether both subgroups benefitted similarly from the given dosing recommendations.

For responses counted as transfusion reduction only 1 of 7 ESA-treated patients had a >50% reduction in transfusions.

In contrast to ESA-naïve patients with RA or RARS classes, patients with RARS in the ESA-treated stratum had mean decreases of Hb from baseline of 0.2-0.3 g/dL.

The enrolment of only 9 patients into phase IIIb study 20130113 did not generate evaluable clinically relevant efficacy and safety data beyond 73 weeks darbepoetin treatment in MDS patients.

As Study 20090160 excluded subjects who had received a total of ≥4 units of RBCs during either of 2 consecutive 8-week periods before randomization or had received any RBC transfusion within 14 days before randomization, and Study 20030207 had few subjects with transfusions within the 3 months before enrolment, the efficacy of darbepoetin alfa in patients with a high transfusion demand has not been evaluated. This is acceptable because the proposed indication is for patients with low- to intermediate-1 risk MDS who have low transfusion demand

Risks

Unfavourable effects

In the Primary Treatment Period (week 1 to week 25 resp. 27/28) the most frequently affected system organ classes (SOC) of adverse events were general disorders and administration site conditions (48.0% darbepoetin alfa, 29.2% placebo) and musculoskeletal and connective tissue disorders (33.6% darbepoetin alfa, 25.0% placebo). In the Extended Treatment Period (week 25 to week 72/end of treatment resp. week 27/28 to week 53/end of treatment) the most affected SOCs were general disorders and administration site conditions (25.0% Q3W, 33.0% Q2W). The second most affected system organ class was infections and infestations (21.4% Q3W, 28.3% Q2W).

Hypertension (incl. hypertensive crisis), thromboembolic events, convulsions, allergic reactions (hypersensitivity), antibody-mediated pure red cell aplasia, cerebrovascular disorders, transient ischemic attacks and heart failure and tumour progression (including mortality) are known identified / potential risk for the approved indications. Most of these adverse events were documented for the treatment of patients with MDS as well and the incidences seem to be consistent with the known safety profile of darbepoetin alfa. In study 20090160 these adverse events were documented somewhat more often in the placebo arm compared to the darbepoetin alfa arm.

Based on the safety database review and signal detection from external spontaneous safety databases, a possible causal relationship between the administration of darbepoetin alfa and severe cutaneous reactions, including SJS/TEN and erythema multiforme is assumed. Severe cutaneous adverse reaction events were reported in 7 of 304 subjects (2.3%) receiving darbepoetin alfa and 1 of 48 subjects (2.1%) receiving placebo during the Primary Treatment Period and 9 of 331 subjects (2.7%) of subjects receiving darbepoetin alfa during the Extended Treatment Period. The issue is currently under assessment in an additional type II variation (EMEA/H/C/000332/II/0141).

Uncertainty in the knowledge about the unfavourable effects

Since no information indicating relatedness of AEs/SAEs, in particular of AEs/SAEs that are considered potential or identified risks in other indications is provided, a full evaluation of the safety profile is not possible at this stage. Information regarding the severity of the documented AEs is incomplete as well.

Furthermore it should be clarified why AE/SAEs that constitute pharmacological class effects considered important identified or important potential risks are not included in SmPC section 4.8 for MDS.

In addition due to differences in the study design and study populations in the submitted studies the presented integrated safety data need to be interpreted cautious:

The study population of the Phase II study (20030207) included patients that were ESA pre-treated as well as ESA naïve ones. In contrast, in the pivotal study (20090160) ESA pre-treated patients were explicatively excluded due to safety reasons. Thus currently the safety in the two subgroups (ESA pre-treated and ESA naïve patients) cannot be assessed separately and thus is uncertain.

In both trials a change from a three-weekly dose scheme (500 µg Q3W) to a two-weekly dose scheme (500 µg Q2W) was allowed. While in general dose titration for ESAs is acceptable, the rules for dose adjustment were different in the studies: Study 20030207 allowed a dose adaption starting from week six, in Study 20090160 dose adjustment was allowed only from week 31. In addition the different dosing schemes (2-weekly versus 3-weekly) resulted in different visit schedules. Currently the safety of the two dosing subgroups can be assessed separately only for the extended treatment period, while

in the safety data presented for the Primary Treatment Period include pooled data from both treatment schemes. If and to what extent different visit schedules may have impacted adverse event reporting is uncertain as well.

The strategy to document disease progression to AML was different: In general progression to AML resulted in withdrawal from the studies. However, in Study 20030207 progressions to AML had to be documented and reported as serious adverse event. In Study 20090160 the progression to AML was documented as well but separately, neither as adverse nor as serious adverse event. This leads to uncertainties in the interpretation of progression data. In addition the long-term follow-up period of the main study (20090160) is still ongoing. Thus the so far presented results are regarded as immature and should be updated. The demanded data available from MDS registries (Scientific Advice EMEA/H/SA/3443/1/2016/II) was not submitted either. In summary, currently the presented information on progression to AML is incomplete and difficult to survey. Thus a full evaluation is not possible at this stage. A statement in the SmPC (section 4.4) on potential progression to AML is missing as well.

Effects Table

Table 1. Effects Table for Aranesp (MDS) (data cut-off: 18.02.2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Hematological improvement						
Increased erythroid response	Erythroid response rate (Studies 20030207 and 20090160): Achieving an initial ≥ 1. g/dL increase in hemoglobin from baseline and sustaining an average rise of ≥ 1.5 g/dL in a rolling 56-consecutive day period in the absence of RBC transfusion	Change in %	20030207[a] Weeks 1 to 13: ESA-naïve 49% (95% CI: 40, 57; 70/144 subjects) ESA-treated 26% (95% CI: 15, 37; 16/62 subjects) Weeks 1 to 28: ESA-naïve 58% (95% CI: 50, 66; 84/144 subjects) ESA-treated 31% (95% CI: 19, 42; 19/62 subjects) Weeks 1 to 52: ESA-naïve 59% (95% CI: 51, 67; 85/144 subjects) ESA-treated 34% (95% CI: 22, 46; 21/62 subjects) 20090160 DBTP[b] Weeks 1 to 25 DA 14.7% (95% CI: 7.56, 24.73; 11/75 subjects) PBO 0% (0/35 subjects); p = 0.016 20090160 ATP[b,d] Weeks 26 to 72/73 DA total 34.7% (34/98 subjects) DA-DA 33.3% (95% CI: 22.4, 45.7; 23/69 subjects) PBO-DA 37.9% (95% CI: 20.7, 57.7; 11/29 subjects) Treatment difference OR: 0.82 (95% CI: 0.33, 2.02; p = 0.66)		Strengths: • Total of 342 subjects have been treated with DA; of these, 146 received IP in a randomized, double-blind, placebo-controlled trial and 128 enrolled in LTFU studies. • In Study 20090160, long-term clinical data (randomized, blinded, placebo-controlled) helped minimize bias in the estimation of treatment effects and statistically significant treatment effect in DA versus PBO. • Nonsponsored, peer-reviewed published meta-analysis supports data. • No overall differences in efficacy were observed when comparing subjects ≥ 75 years of age versus subjects < 75 years of age. Limitations: • Limited generalizability of trial data to the more heterogeneous population of patients who might receive DA in the postmarketing setting. • A comparator arm was not used in Study 20030207, LTFU of Study 20090160, and	20030207 CSR Table 14-9, Table 14-9.2, and Table 14-9.4 20090160 Primary CSR Table 14-4.6.1 20090160 Interim CSR Table 14a-4.6.1

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					Study 20130113. • Study 20030207 had descriptive data only (uncontrolled) Uncertainties: • There is only 1 placebo-controlled trial. Magnitude of treatment effect on increased hemoglobin between DA and PBO were not analyzed.	
Reduction in RBC transfusions	Incidence of RBC transfusions (Studies 20030207 and 20090160) Incidence of at least 1 RBC transfusion from week 5 to the end of the 24-week double-blind treatment period	Change in %	20030207[c] Weeks 1 to 13: ESA-naïve 17% (95% CI: 11, 23; 24/144 subjects) ESA-treated 35% (95% CI: 22, 47; 20/62 subjects) Weeks 1 to 28: ESA-naïve 18% (95% CI: 12, 25; 26/144 subjects) ESA-treated: 37% (95% CI: 24, 50; 21/62 subjects) Weeks 1 to 52: ESA-naïve 28% (95% CI: 20, 36; 37/144 subjects) ESA-treated: 42% (95% CI: 29, 56; 23/62 subjects) 20090160 DBTP Week 5 to EOTP DA 36.1% (35/97 subjects) PBO 59.2% (29/49 subjects); p = 0.008 20090160 ATPd (Week 5 to EOATP) DA total 60.3% (76/126 subjects) DA-DA 59.8% (52/87 subjects) PBO-DA 61.5% (24/39 subjects); p = 0.85		Strengths: • Reduced number of RBC transfusions was seen in subjects treated with DA versus PBO (Study 20090160). • No overall differences in efficacy were observed when comparing subjects ≥ 75 years of age versus subjects < 75 years of age. Limitations: • Limited generalizability in diverse populations in all studies. • A comparator arm was not used in Study 20030207, LTFU of Study 20090160, and Study 20130113. • Study 20030207 had descriptive only (uncontrolled). Uncertainties: • Uncertainty on the strength of the effect on RBC transfusions arises as more patients in the placebo arm received 3 and more units RBC in the 16 weeks prior to randomisation (30.6% vs. 20.6%) indicating a higher transfusion need at baseline • There is only 1 placebo-controlled trial.	20090160 Primary CSR Table 14-4.1.1 20090160 CSR Table 14a-4.1.1
Unfavourable Effects						
Known identified / potential risks						
Hypertension	Subject incidence of hypertension (Studies 20030207 and 20090160). Identified risk based on class effects and risks reported in the oncology	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 8/304 subjects (2.6%) PBO: 2/48 subjects (4.2%)		Uncertainties: No information indicating relatedness of AEs/SAEs, in particular of AEs/SAEs that are considered potential or identified risks in other indications is provided, a full evaluation of the	SCS Table 10

Effect	Short Description	Unit	Treatment Control	Uncertainties / Strength of evidence	References
	indication in other clinical trials.		**Extended treatment phase** 6/331 subjects (1.8%)	safety profile is not possible at this stage	
Embolic and thrombotic events	Subject incidence embolic and thrombotic events (Studies 20030207 and 20090160). Identified risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 4/304 subjects (0.3%) PBO: 0/48 subjects **Extended treatment phase** 10/331 subjects (0.9%)	Due to differences in the study design and study populations the presented integrated safety data need to be interpreted cautious – further post hoc analysis to evaluate the safety profile properly are required The strategy to document disease progression to AML was different. In general progression to AML resulted in withdrawal. However in the Phase II study (20030207) progression to AML had to be documented and reported as serious adverse event. In the pivotal Study (20090160) the progression to AML was documented as well but separately, neither as adverse nor as serious adverse event. This leads to uncertainties in the interpretation of progression data.	SCS Table 10
Arterial thromboembolic events	Subject incidence arterial thromboembolic events (Studies 20030207 and 20090160). Identified risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 2/304 subjects (0.7%) PBO: 0/48 subjects **Extended treatment phase** 4/331 subjects (1.2%)		SCS Table 10
Cerebrovascular disorders	Subject incidence of cerebrovascular disorders (Studies 20030207 and 20090160). Potential risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 3/304 subjects (1.0%) PBO: 1/48 subjects (2.1%) **Extended treatment phase** 8/331 subjects (2.4%)		SCS Table 10
Cardiac failure	Subject incidence Cardiac failure (Studies 20030207 and 20090160). Potential risk based on class effects and risks reported in the nephrology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 35/304 subjects (11.5%) PBO: 5/48 subjects (10.4%) **Extended treatment phase** 4/331 subjects (1.2%)		SCS Table 10
Ischaemic heart disease	Subject incidence Ischaemic heart disease (Studies 20030207 and	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 3/304 subjects		SCS Table 10

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	20090160). Potential risk based on class effects and risks reported in the nephrology indication in other clinical trials.		(1.0%) PBO: 1/48 subjects (2.1%) **Extended treatment phase** 4/331 subjects (1.2%)			

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Hypersensitivity	Subject incidence hypersensitivity (Studies 20030207 and 20090160). Identified risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 46/304 subjects (15.1%) PBO: 6/48 subjects (12.5%) **Extended treatment phase** 37/331 subjects (11.2%)			SCS Table 10
Antibody-mediated PRCA	Subject incidence ofantibody-mediated PRCA (Studies 20030207 and 20090160). Potential risk in oncology and identified risk in nephrology based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	No adverse events of antibody-mediated PRCA were reported in any MDS study to date.			n.a.
Convulsions	Subject incidence of convulsions (Studies 20030207 and 20090160). Identified risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 1/304 subjects (0.3%) PBO: 0/48 subjects **Extended treatment phase** 0/331 subjects			SCS Table 10
Mortality in patients with history of cancer	Subject incidence of fatal adverse events related to subjects with a history cancer. Potential risk based on class effects and risks reported in the oncology indication in other clinical trials.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 8/304 subjects (2.6%) PBO: 2/48 subjects (4.2%) **Extended treatment phase** 7/331 subjects (2.1%)			SCS Table 6
Progression to AML	Subject incidence of progression to AML. Potential risk based on effects identified in MDS trials.	Change in %	20090160 **Primary treatment phase** DA: 2/304 subjects (2.1%) PBO: 1/48 subjects (2.2%) **Extended treatment phase** 2/331 subjects (2.3%) **Long term follow-up** 5/128 subjects (3.9%)			Table 12-5 (Study 20090160 primary analysis) Table 14a-11.1.3 (study 20090160

Effect	Short Description	Unit	Treatment Control	Uncertainties / Strength of evidence	References
			200302017 Progression to AML was not collected 6/206 subjects (2.9%)		interim analysis) SCS section 2.1.4.3.1 and 2.1.4.3.2 Listing 16-11-1-1 ISS
New identified risk (currently under assessment in an additional variation)					
Severe cutaneous reactions	Subject incidence of severe cutaneous reactions.	Change in %	Pooled 20030207 and 20090160 **Primary treatment phase** DA: 7/304 subjects (2.3%) PBO: 1/48 subjects (2.1%) **Extended treatment phase** 9/331 subjects (1.2%)	Uncertainties: No information indicating relatedness of AEs/SAEs, in particular of AEs/SAEs that are considered potential or identified risks in other indications is provided, a full evaluation of the safety profile is not possible at this stage Due to differences in the study design and study populations the presented integrated safety data need to be interpreted cautious – further post hoc analysis to evaluate the safety profile properly are required	CSC page 47
Most frequently affected system organ classes					
General disorder	Subjects incidence of General disorders	Change in %	**Primary treatment phase** DA: 146/304 subjects (48.0%%) PBO: 14/48 subjects (29.2%) **Extended treatment phase** 98/331 subjects (29.6%)	Uncertainties: No information indicating relatedness of AEs/SAEs, in particular of AEs/SAEs that are considered potential or identified risks in other indications is provided, a full evaluation of the safety profile is not possible at this stage	Table 14-6.2.1 ISS
Musculoskeletal disorder	Subjects incidence of Musculoskeletal disorde	Change in %	**Primary treatment phase** DA: 102/304 subjects (33.6%) PBO: 12/48 subjects (25%) **Extended treatment phase** 73/331 subjects	Due to differences in the study design and study populations the presented integrated safety data need to be interpreted cautious – further post hoc analysis to evaluate the safety profile properly are required	Table 14-6.2.1 ISS

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			(22.1%)			
Infections and infestations	Subjects incidence of Infections and infestations	Change in %	**Primary treatment phase** DA: 88/304 subjects (28.9%) PBO: 14/48 subjects (29.2%) **Extended treatment phase** 84/331 subjects (25.4%)			Table 14-6.2.1 ISS

Benefit-Risk Balance

Importance of favourable and unfavourable effects

For MDS patients who suffer from MDS-related anaemia fatigue is one of the major symptoms resulting in a reduced quality of life. Fatigue was the most often reported AE in the pivotal study and this was even reported with a >10% higher frequency in darbepoetin-treated than in placebo patients (in the pooled analyses). As derived from the HRQOL questionnaires, the administration of darbepoetin 500µg Q3W did not lead to a clinically relevant improvement of this anaemia-related fatigue. Only an increase of the dosing frequency to Q2W in the open-label phase that led to Hb responses was capable to improve this symptom, which was then measurable by the FACIT-F scale.

During early national scientific advice from the Rapporteur Germany transfusion reduction was seen as the clinically most relevant primary efficacy endpoint in the MDS population, in contrast to a moreless pharmacological endpoint of Hb increase. This advice was initially not taken into consideration by the MAH. Only a very late change of the primary endpoint resulted in analysis of incidence of transfusions as the primary objective. The change of the endpoint was performed when during programming of tables in preparation of the CSP it was observed that the initial primary endpoint, erythroid response according to IWG 2006, would not be reached. The change of the primary endpoint shortly before end of study enrolment results in serious doubts of blinded review. This also raises the question whether the dosing of 500µg Q3W was adequate in this study population. Therefore, even if RBC transfusions were statistically significantly reduced compared to placebo for the “new” primary endpoint, this is questioned.

The dose planning was done on basis of the results of the phase II study 20030207 that used this dosing; however there, dose increases at earlier timepoints starting from 6 weeks after treatment initiation could have been performed. Also, in Appendix F of the pivotal CSP the MAH referenced several other studies which investigated higher doses, e.g., 150µg QW, 300µg QW. The MAH also referenced a meta-analysis of Park et al., 2016, which concluded that common darbepoetin doses were 150-300µg QW. Hence, the low performance of the chosen 500µg Q3W dose over a test period of 25 weeks could be seen as having withheld efficacious treatment from the study patients. During the national scientific advice meeting in November 2014 the MAH suspected that the used dosing regimen was not adequate for the IWG 2006 response criteria. This, however, is not a fault of the current common response criteria but of an inadequate study planning.

ESA-pretreated patients, which were only investigated in the phase II US-study, had pre-study epoetin or darbepoetin doses that were often higher or more frequent than 500µg darbepoetin Q3W. So, an

early withdrawal of Informed Consent and receipt of less than 4 weeks of treatment in 15% of ESA-pretreated patients is not unexpectable, but is a marker for a too low dose.

Overall, transfusion reduction and erythroid response are important factors to improve QoL and survival of lower-risk MDS patients. With treatment of anaemia also other symptoms despite fatigue should have been reduced, such as weakness and shortness of breath. This was not established. In general, the pooled safety data were not thoroughly assessable because treatment-naïve and pretreated patients were pooled.

In addition, it is unassessable, but probable, that the different visit schedule of 2-weekly in the Q2W treated patients also led to increased reporting frequencies for AEs compared to the 3-weekly schedule in Q3W treated patients.

As could be expected from published treatment data, only patients with a baseline serum epo level of <100mU/ml showed Hb responses, for the other baseline epo groups clinically relevant efficacy was not established. Therefore, also safety has to be analysed separately for baseline epo levels to evaluated benefit risk in this subgroup accordingly.

In general, there were no data for ESA-pretreated patients from the EU, therefore it is questionable whether these data are valid to be used in the underlying variation for a European indication in this population.

Benefit-risk balance

The benefits with regard to transfusion reduction or erythroid response observed in the confirmative double-blind setting of the pivotal phase III study are lower than what was expected by the MAH during statistical planning, what could be expected when published data are reviewed, and also what was observed in the open-label phase and the preceding phase II study. This is unquestionably due to the fixed 500µg Q3W dosing regimen in the double-blind phase. In comparison to the obtainable efficacy seen with higher doses or under higher frequency the benefit established here is low.

However, several analyses related to prognostic subgroups as well as other analyses were not performed or not submitted to be able to evaluate the benefits. Notably, the questionable GCP conformity with change of the primary endpoint and resultant 2 concurrent valid study protocols preclude generally from any final conclusions.

The benefit is, furthermore, also lower than observed in the phase III study with epoetin alpha (Erypo, study EPOANE3021) in a fully comparable ESA-naïve MDS population that led to extension of the indication for lower-risk MDS patients in early 2017. In that study responses were also measured according to IWG 2006 criteria but dosing was weight-based, not fixed, and dose increases were allowed from week 8 ongoing.

Neither, the efficacy of the Q3W regimen was not good enough to show a reduction of the most important anaemia symptom fatigue, as also measured by HRQOL questionnaires, but fatigue was very commonly reported as AE.

Furthermore, it is currently not possible to adequately assess the safety profile due to the inadequate presentation in the dossier. As such, it is currently not assessable whether the increased AE frequency under “some” Q2W dosing is due to the similarly increased visit frequency or a result of the dose frequency itself.

Discussion on the Benefit-Risk Balance

In general, a "legalisation" of Aranesp in the indication of treatment of MDS-related anaemia in the EU would be highly acknowledged because darbepoetin is currently often used off-label and EU treatment guidelines, e.g., ESMO clinical practice guidelines, support its [ESA] use with "*weekly doses of 150-300µg darbepoetin … when the baseline EPO level is low and transfusion requirement is absent or limited*".

In fact, though MDS is an orphan disease and for long no medicinal product was approved to treat symptomatic anaemia, since recently EU patients do not have a high medical need because epoetin alpha was approved in 2017 for this indication. As epoetin was investigated in both ESA-naïve and ESA-pretreated EU MDS-patients and established its benefit according to IWG 2006 criteria, for a comparable darbepoetin indication comparable study data are necessary for a positive benefit-risk balance.

However, the data basis analysed and submitted for this extension of indication variation from the pivotal phase III EU study 20090160 in ESA-naïve MDS patients and the supportive US-study 20030270 in ESA-naïve and ESA-pretreated patients is presently not considered sufficient to conclude on a positive benefit-risk profile of darbepoetin. In fact, at present the assessor is not sure whether the results from the triggered GCP inspection could completely rule out the different doubts.

The indication proposed by the MAH is not approvable based on these data.

4. Recommendations

The application for:

Extension of Indication to include treatment of anaemia in adult patients with low transfusion demand in low or intermediate-1-risk myelodysplastic syndromes for Aranesp; as a consequence, sections 4.1, 4.2,4.8, 5.1 and 5.2 of the SmPC are updated in order to update the safety and efficacy information. The Package Leaflet is updated in accordance. Updated RMP version 8.0 has been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce QRD editorial changes in the SmPC, Annex IIIA and Annex IIIB.

☒ is not approvable since major objection and other concerns have been identified, which preclude a recommendation at the present time.

The details of these major objections and other concerns are provided in Annex 1 (RSI 1) and should be addressed in writing

Proposal for inspection

A triggered GCP inspection is requested by the Rapporteur for the pivotal phase III clinical studies 20090160. The outcome of this inspection and the satisfactory responses to its findings will be needed with the responses to 1st RSI.

Triggers of request of GCP inspection pertain (at least) the following:

Study 20090160:

- The biometrical major objection regarding data-driven change of primary endpoint at the end of enrolment due to informative (though blinded) data review. To our understanding this data review did not take place within a SOP-controlled Blind Review or a SOP-controlled Review of the Data Monitoring Committee, therefore comprehending of the process resulting in the change of the primary endpoint is considered necessary.
- High number of patients excluded from the distinct primary analyses and uncertainties regarding safety evaluation (e.g. relatedness of AEs).
- Verification of the data regarding the incidence of RBC transfusions, the erythroid response rates and the safety information. Comparability of these aspects when different visit schedules were necessary.

Annex 1: Rapporteur proposed Request for Supplementary Information

Non clinical aspects

Major objections

None

Other concerns

1. Since the applicant applies for an additional indication an increase in environmental exposure can be expected and thus an environmental risk assessment for the active ingredient darbepoetin alfa should be provided.

Clinical pharmacology aspects

None

Clinical efficacy aspects

Major Objections

Biometrical:

2. The modalities and consequences of the data-driven change of the primary endpoint remain unclear and question the validity of the primary analysis with respect to

    a. The resulting impact on type-I-error: A not pre-specified decision-strategy was used for changing the primary endpoint. The MAH is asked to show that the type-I-error for the overall-procedure is controlled.
    b. The two conflicting effective versions of the CSP and two conflicting SAPs and the resulting equivocal criterion for success of the trial. The MAH is asked to provide a scientific rational, why the non-conformity to ICH-GCP standards could be acceptable in this application.

3. The high number of patients excluded from the distinct primary analyses, the absence of a thorough discussion of potentially introduced bias (possible overestimation of efficacy) and the absence of robustness analyses with different handling of missing values further question the robustness of the trial results. The MAH is asked to discuss the issue of robustness in the light of missingness and handling of missing values

Clinical

4. The efficacy and safety results for the intended EU indication for treatment of ESA-pretreated MDS patients originate from a single-arm, open-label, descriptive phase II study, conducted 2004-2006 in the US (20030207) that included patients that are not in full concordance with current European treatment recommendations for Low/Int-1-risk MDS patients regarding the following criteria:

    - baseline Hb-value
    - MDS-classifications / prognostic profiles
    - baseline RBC transfusion status
    - endogenous baseline epoetin level

    The MAH should justify that the data are fully transferable to the intended European MDS population.

Other concerns

5. The statement about non-EU studies in Module 1.9 refers to a wrong drug substance. The MAH is requested to resubmit a corrected statement.

Study 20030207

6. Treatment failures were defined in CSP but not reported. The MAH should clarify the patients who qualified as treatment failures.
7. The MAH is asked to provide information about dose increases or decreases after week 6 and the changes from Q3W to Q2W in both strata during the extended treatment period, including the referenced evaluation of response by dosing scheme.
8. The MAH should discuss possible differences in (early) responses between epoetin and darbepoetin-pretreated patients and whether the proposed fixed (starting)-dose recommendation of 500µg Q3W (e.g., in contrast to a weight-based dosing or a Q2W frequency) has similar benefit in both groups, especially when switching the ESA.

Study 20090160

9. Biometrical concerns pertain the following:
    a. The quality of the data of the primary endpoint is unclear since it is unknown whether the same monitoring did apply for each of them for the whole time.
    b. Blind Review Report(s) are missing, but needed.
    c. A statement, when the database lock was activated.
    d. Missing primary analysis for the German primary parameter based on a pre-defined per-protocol set.
    e. A sensitivity analysis for the primary endpoint for Germany based on more relaxed responder criteria is considered useful.

10. Concerning the primary endpoint RBC transfusion: Additional subgroup and/or sensitivity analyses with adequate discussion are requested:

    a. For endogenous serum baseline epo levels as currently divided (</≥100mU/ml). In addition, the MAH should give details about number of patients with Epo levels <200mU/ml and additional subgroup analysis for epo levels </≥200mU/ml.

    b. For WHO classes

    c. For time to first RBC and time to first RBC after week 5 including corresponding K-M curves.

11. Concerning the secondary endpoint erythroid response: Additional subgroup and/or sensitivity analyses with adequate discussion are requested:

    a. For baseline Hb-subgroups. In addition, to use local baseline Hb values, as available, for the patients currently counted as “not evaluable”.

    b. For WHO classes.

    c. For time to erythroid response and duration of response.

    d. Please provide a tabulation of the underlying analysis sets with regard to the previous primary endpoint erythroid response, i.e. “analysis for Germany”.

12. Concerning the active treatment (open label) phase:

    a. Please clarify when and how unblinding was performed after the DBTP

    b. The MAH should provide and discuss data for transfusions and erythroid responses only for the active treatment phase to be able to compare effects of dosing regimens.

    c. The deleted analysis “For the subgroup of subjects who receive a dose escalation to 500 µg Q2W during the active treatment period, summary statistics will be generated for selected haemoglobin, transfusion, and safety endpoints in order to explore the impact of the dose adjustment.” should be reinitiated to evaluate all the mentioned points, and include time of dose change and further dose adjustments, e.g. due to excessive Hb increase.

    d. Five subjects with erythroid response during the open label period had a baseline serum endogenous erythropoietin level of >100 mU/mL. Please provide details about dosing frequency and WHO class of these 5 patients.

13. The applicant is asked to thoroughly evaluate reasons for the obvious differences in erythroid responses in the DBTP between preceding studies and the pivotal study to justify the proposed dosing recommendation of Q3W 500µg darbepoetin. Hereby, the MAH should also justify the proposed dose increase recommendations in section 4.2 based on single-arm open-label phase data only.

14. The MAH should comment on the sensitivity and specificity of the anti-darbepoetin antibody assay as in 143 patients antibodies were detected, although they were included as without any prior ESA-treatment.

15. For an additional clarification of the large number of patients in study 20090160 for whom there was no central lab baseline Hb value (14/49, 29% placebo and 22/97, 23% darbepoetin) available and to exclude a systematic reason for the missing data, the applicant is asked to provide further information about the sites these patients were from and about the reasons why the mentioned data were not collected (Member state 1 comment).

16. Concerning the between-study comparisons:

    a. The MAH should compare the 24-week DBTP with the 28-week treatment period of study 20030207. It should be justified why this was not considered more informative.

    b. The open-label phase of study 20090160 should be compared against the phase II study as for both dose increases to Q2W were allowed.

    c. Further between-study analyses and discussion should be performed for baseline prognostic scores such as IPSS, FAB classification, WHO classification, EPO-level, Hb level, bone marrow blasts.

17. Concerning the supportive study 20130113:

    a. The MAH should also clarify whether the patients with >2 doses were on Q2W or Q3W dosing.

    b. The enrolment of only 9 patients in 5 sites into a long-lasting treatment phase is a missed chance to generate clinically relevant efficacy and safety data beyond 73 weeks for darbepoetin in MDS patients. The MAH should discuss why this was not performed as planned and give a proposal how to generate such data instead.

SmPC/PL

18. The proposed wording in section 4.2 should be reworded to reflect a “common SmPC recommendation phrasing”, as currently it reflects the obligatory wording of a study protocol “dose is escalated” or “reduction is permitted”.

19. No user testing was performed for the amended PL and no justification is provided. The MAH is asked to submit a respectively completed module 1.3.

Clinical safety aspects

Major Objections

None

Other concerns

20. The applicant is asked to submit a post hoc safety analysis which compares the two different schemes (Q2W vs Q3W) as well as the different populations (ESA naïve and ESA pre-treated patients). If and to what extent different visit schedules may have impacted adverse event reporting is uncertain. The MAH is asked to comment.

21. Currently the safety analysis in the subgroup of ESA pre-treated patients cannot be assessed separately. Further analyses addressing the safety in ESA pre-treated patients are necessary.

22. Since not found in the documentation of the Phase II study (20030207) data regarding dose reduction and dose withheld is requested.

23. Since not found in the documentation, the applicant is asked to present grades (Grade 1-5) of the

incidences of adverse events in the Phase II study (20030207).

24. Since not found in the documentation as well, a table indicating related AEs should be provided together with a discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

25. Regarding the high level group term of thromboembolic events (venous and arterial) the applicant is asked to submit an additional safety analysis for patients with an Hb <11 mg/dl versus patients with an Hb >11 mg/dl.

26. Since the responses apparently depend on endogen epoetin levels at baseline, the applicant is asked to present additional safety analysis for patients with low versus high serum epoetin levels (cut-off 100 mU/ml, 200 mU/ml).

27. The total number of SAEs was not found and should be provided for both studies.

28. In the primary treatment period only for gastrointestinal SAEs a difference in frequency of 2% or more was observed (in the primary treatment period 8 SAEs with darbepoetin versus 0 SAEs in placebo arm, extended treatment period further 7 SAEs). A discussion of the gastrointestinal SAEs should be provided.

29. Since not found a table indicating related SAEs should be provided together with a resp. discussion on causal relationship, in particular for AEs that are considered potential or identified risks in other indications.

30. It should be clarified why AE/SAEs that constitute pharmacological class effects considered important identified or important potential risks are not included SmPC section 4.8 for MDS, e.g. thromboembolic events.

31. In the pivotal study (20090160) 7 patients died from disease progression to AML. From the narratives it appears that none of the deaths was considered related to treatment by the investigator. The MAH should state potential causal relationships.

32. The applicant is asked to present the information on MDS progression, progression to AML, progression to non-AML acute leukemia by time/treatment period and treatment arm in a table.

	Total MDS Progression		Progression to AML		Progression to non AML acute leukemia	
	Placebo	Darbepoetin alfa	Placebo	Darbepoetin alfa	Placebo	Darbepoetin alfa
Safety analysis set						
Double-blind period						
Aktive treatment Period						
Long-term follow-up						
Total						

33. In addition the following issues should be presented in form of a table: Patient (Identifier, Age, Sex); Treatment scheme (2-weekly / 3-weekly); Pre- treatment (ESA pre-treated / ESA naïve);

Change in IPSS risk category; Change in MDS classification; time on study at progression.

34. The applicant is requested to discuss these data. Furthermore, the applicant is asked to present all data available from MDS registries (SA EMA, EMEA/H/SA/3443/1/2016/II).

35. Concerning module 2.5 Clinical Overview Appendix 1: the effects table should be updated for the unfavourable effects with a listing splitted in line with the responses to questions 20, 21 and 24. In addition, the currently referenced post-hoc tables 14-1.1 ff for the unfavourable effects have to be submitted.

36. The reason for the imbalance in the subject incidence of fatigue between treatment groups favouring placebo (pivotal study 20090160) is unknown. It is a rather surprising finding as one would expect less fatigue in the active treatment group. The Applicant should elaborate on this (OC 1 Co-Rapporteur).

37. Regarding the presented data there is uncertainty about the unfavourable effects on the very long term. As there is a theoretical risk that darbepoetin promotes malignancies, the applicant is asked on which base this risk can be ruled out (OC 2 Co-Rapporteur).

RMP

38. No adverse events of vascular access thrombosis were reported in any MDS study to date. However as it is an identified risk in other indications it should be observed /monitored in MDS as well. Hence the MAH is asked also to include it as important potential risk for the MDS.

39. Events of ischemic heart disease, including myocardial infarction were observed in studies with MDS patients. Hence this safety concern should also be defined for the MDS indication.

40. “Safety related to higher doses administered in patients with CRF (nephrology indication only)” has been deleted by the MAH due to finalization of a Meta-analysis for re analysis of clinical trial data concerning hemoglobin levels and ESA doses in CRF patients. The MAH is asked to provide a very short summary about the main outcomes/ conclusions drawn on this study which would help to conclude on whether or not deletion from Missing Information is justified.

41. The MAH states that “(…) the safety and efficacy of darbepoetin alfa have not been established in pediatric patients with cancer or MDS (…)”. Hence, both cancer and MDS indications are restricted to adults. In conclusion, it is not overall agreed with the MAH to completely delete “Paediatric patients” from the table. No paediatric data have been submitted for the MDS indication. For that reason, for the time being this safety concern should remain in the table for cancer and MDS indication.

42. (Following MS comment): The CHMP has asked for an additional analysis of thromboembolic events. Dependent of the outcome of this analysis it should be considered that this safety concern may also be applicable to the MDS indication. The MAH is therefore asked also to consider thromboembolic events as important risk for MDS. Following the outcome of CHMP’s requested analysis the MAH is asked to adequately address the risk for MDS as either important potential or important identified risk.

SmPC/PIL:

43. AEs that are considered potential or identified risks in other indications as well as adverse events of special/historical interest that were observed in MDS patients should be included in section 4.8,

unless otherwise justified. In addition in section 4.4 a statement on potential progression to AML should be included.

Annex 3: Product Information annotated with Rapporteur comments

This Annex is circulated as a separate document.