



Clinical trial results:

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

Summary

EudraCT number	2010-022884-36
Trial protocol	GR IT BG
Global end of trial date	07 January 2016

Results information

Result version number	v1
This version publication date	01 January 2017
First version publication date	01 January 2017

Trial information

Trial identification

Sponsor protocol code	EPOANE3021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01381809
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to demonstrate that epoetin alfa treatment is better at improving anemia outcome (as evaluated by erythroid response – International Working Group [IWG] 2006 criteria; ie, an increase in hemoglobin by at least 1.5 gram per deciliter (g/dL) or a relevant reduction of red blood cell (RBC) units transfused by an absolute number of at least 4 units every 8 weeks; responses must last at least 8 weeks) in subjects with International Prognostic Scoring System (IPSS) low- or intermediate-1-risk myelodysplastic syndromes (MDS) compared with placebo through Week 24.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations were based upon Thrombotic vascular events; Relapse after hematologic improvement and disease progression, Loss of response to study agent, Clinical laboratory tests, physical examinations, vital signs. Adverse events (AEs) were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Russian Federation: 5
Worldwide total number of subjects	130
EEA total number of subjects	125

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	104
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 186 potential subjects were screened for enrollment into the study and 130 subjects were randomly assigned to one treatment group (85 subjects to Epoetin Alfa and 45 subjects to Placebo). Out of them, 93 subjects have completed the study (60 subjects from Epoetin Alfa and 33 subjects from Placebo arm).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoetin Alfa

Arm description:

Subjects received a Starting dose of 450 International Unit per kilogram (IU/kg) of Epoetin Alfa (maximum total dose of 40,000 IU) administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.

Arm type	Experimental
Investigational medicinal product name	Epoetin Alfa
Investigational medicinal product code	EPO
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a Starting dose of 450 (IU/kg) of Epoetin Alfa (maximum total dose of 40,000 IU) administered subcutaneously up to Week 48.

Arm title	Placebo
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Arm description:

Subjects received a Starting dose of a matching volume of placebo were administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a Starting dose of a matching volume of placebo were administered subcutaneously once every week up to Week 48.

Number of subjects in period 1	Epoetin Alfa	Placebo
Started	85	45
Completed	60	33
Not completed	25	12
Adverse event, serious fatal	3	-
Consent withdrawn by subject	6	3
Physician decision	-	1
Non responder	3	1
Adverse event, non-fatal	2	-
Adverse event, serious non-fatal	7	6
Relapse after hemat imprmnt or disease progression	2	-
Protocol deviation	1	-
Lack of efficacy	1	1

Baseline characteristics

Reporting groups

Reporting group title	Epoetin Alfa
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Reporting group description:

Subjects received a Starting dose of 450 International Unit per kilogram (IU/kg) of Epoetin Alfa (maximum total dose of 40,000 IU) administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.

Reporting group title	Placebo
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Reporting group description:

Subjects received a Starting dose of a matching volume of placebo were administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.

Reporting group values	Epoetin Alfa	Placebo	Total
Number of subjects	85	45	130
Title for AgeCategorical Units: subjects			
infants and toddlers(28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	4	14
From 65 to 84 years	67	37	104
85 years and over	8	4	12
Title for AgeContinuous Units: years			
arithmetic mean	74.3	74.1	
standard deviation	± 8.62	± 9.25	-
Title for Gender Units: subjects			
Female	39	20	59
Male	46	25	71

End points

End points reporting groups

Reporting group title	Epoetin Alfa
Reporting group description:	
Subjects received a Starting dose of 450 International Unit per kilogram (IU/kg) of Epoetin Alfa (maximum total dose of 40,000 IU) administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a Starting dose of a matching volume of placebo were administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.	

Primary: Percentage of Subjects with Erythroid Response at Any Time During the First 24 Weeks

End point title	Percentage of Subjects with Erythroid Response at Any Time During the First 24 Weeks
End point description:	
Erythroid response was evaluated to demonstrate that epoetin alfa treatment is better at improving anemia outcome (as evaluated by erythroid response – International Working Group [IWG] 2006 criteria; ie, an increase in hemoglobin by at least 1.5 gram per deciliter (g/dL) or a relevant reduction of Red blood cells (RBC) units transfused by an absolute number of at least 4 units every 8 weeks; responses must last at least 8 weeks) in subjects with International Prognostic Scoring System (IPSS) low- or intermediate-1-risk myelodysplastic syndromes (MDS) compared with placebo through Week 24. The modified intent-to-treat (mITT) analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.	
End point type	Primary
End point timeframe:	
Up to Week 24	

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Percentage of Subjects				
number (not applicable)	31.8	4.4		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Epoetin Alfa v Placebo

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Duration of Erythroid Response

End point title	Duration of Erythroid Response
End point description:	
Duration of response (days) was defined by the assessment of the Response Review Committee (RRC) for subjects who responded at any time during the first 24 weeks of the study. The duration of response was defined as the number of days from the date of the week at which the response started until the date of the week the response ended +1 day. The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.	
End point type	Secondary
End point timeframe:	
Up to Week 24	

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Days				
median (full range (min-max))	197 (54 to 323)	99 (50 to 148)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Erythroid Responders at Week 48

End point title	Percentage of Subjects With Erythroid Responders at Week 48
End point description:	
The percentage of responders at Week 48 was calculated using the RRC assessment of erythroid response: the number of subjects who responded at Week 48 divided by the total number of subjects in the given analysis data set for each treatment group. Responders at Week 48 were defined as subjects who were responders at Week 24, continued the study treatment, and maintained their response status through Week 48. The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Percentage of Subjects				
number (not applicable)	9.4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Red Blood Cell (RBC) transfusion

End point title	Time to First Red Blood Cell (RBC) transfusion
End point description:	
The analysis population is subjects with at least one RBC transfusions either in the 8 weeks prior to baseline and/or after randomization. The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.	
End point type	Secondary
End point timeframe:	
Up to Week 52	

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	31		
Units: Days				
arithmetic mean (standard error)	121.9 (± 15.93)	62.3 (± 11.17)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Epoetin Alfa v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.653
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.999
upper limit	2.736

Secondary: Transfusion-Free Intervals

End point title	Transfusion-Free Intervals
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End point description:

Transfusion-free interval is defined as the time (days) from the last visit date minus baseline date plus 1 minus the number of days with transfusions (day on which 1 or more RBC or whole blood units were transfused). The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.

End point type	Secondary
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End point timeframe:

Up to Week 48

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Days				
median (full range (min-max))	191 (41 to 378)	192 (41 to 302)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with RBC Units Transfused

End point title	Percentage of Subjects with RBC Units Transfused
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End point description:

The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.

End point type	Secondary
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End point timeframe:

8 Weeks Prior to Baseline Visit to Week 24

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Percentage of Subjects				
number (not applicable)				
In 8 Weeks Prior to Baseline Visit	51.8	48.9		
Between Baseline and Week 8	36.5	44.4		
Between Week 8 and Week 16	28	51.2		
Between Week 16 and Week 24	24.7	54.1		
Between Baseline and Week 24	42.4	57.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Erythroid Response at Week 24 Based on RRC and CRF Evaluations

End point title	Percentage of Subjects with Erythroid Response at Week 24 Based on RRC and CRF Evaluations
End point description: Erythroid response was evaluated to demonstrate that epoetin alfa treatment is better at improving anemia outcome (as evaluated by erythroid response – International Working Group [IWG] 2006 criteria; ie, an increase in hemoglobin by at least 1.5 gram per deciliter (g/dL) or a relevant reduction of Red blood cells (RBC) units transfused by an absolute number of at least 4 units every 8 weeks; responses must last at least 8 weeks) in subjects with International Prognostic Scoring System (IPSS) low- or intermediate-1-risk myelodysplastic syndromes (MDS) compared with placebo through Week 24. Erythroid Response reported for this endpoint was assessed by Response Review Committee (RRC) and case report form (CRF). The modified intent-to-treat (mITT) analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment.	
End point type	Secondary
End point timeframe: Week 24	

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Percentage of Subjects				
number (not applicable)				
RRC	27.1	2.2		
CRF	36.5	4.4		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Epoetin Alfa v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact test

Statistical analysis title	Statistical analysis 2
Comparison groups	Epoetin Alfa v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact test

Secondary: Change From Baseline in Quality of Life as Measured by Functional Assessment of Cancer Therapy-Anemia/Fatigue (FACT-An) Questionnaire

End point title	Change From Baseline in Quality of Life as Measured by Functional Assessment of Cancer Therapy-Anemia/Fatigue (FACT-An) Questionnaire
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End point description:

The FACT-An questionnaire is used to assess health-related quality of life (HRQoL). It measures the impact of anemia-related symptoms on patient functioning. The overall score range for the FACT-An is 0-188. Higher scores indicate better HRQoL. Patients with higher hemoglobin levels and better performance status reported significantly higher scores on these instruments (including the newly created subscales) than did those with lower hemoglobin levels and poorer performance status. The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment. Here the data value 998, -999 and 999 indicates no data evaluated at specific timepoint for this endpoint. Here, n indicates the number of subjects evaluated at specific timepoint for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 24, Week 48 and up to Early Termination

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
FACT-An: Baseline (n= 74, 38)	125.861 (± 31.2489)	131.837 (± 27.7914)		
FACT-An: Change baseline to Week 24 (n= 66, 34)	-0.626 (± 24.5955)	0.018 (± 18.091)		
FACT-An: Change baseline to Week 48 (n= 29, 0)	7.319 (± 18.2709)	999 (± 999)		
FACT-An: Change baseline to Early Term (n= 15, 34)	-12.006 (± 29.137)	-0.264 (± 25.0688)		

Statistical analyses

Statistical analysis title	Statistical Analysis at Week 24
Comparison groups	Placebo v Epoetin Alfa
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.884
Method	Wilcoxon 2-sample test

Statistical analysis title	Statistical Analysis at Early Termination
Comparison groups	Epoetin Alfa v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.513
Method	Wilcoxon 2-sample test

Secondary: Change From Baseline in Quality of Life as Measured by EuroQol 5-dimension (EQ-5D) Questionnaire

End point title	Change From Baseline in Quality of Life as Measured by EuroQol 5-dimension (EQ-5D) Questionnaire
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End point description:

The EQ-5D is a patient-completed, multidimensional measure of health related quality of life. The instrument is applicable to a wide range of health conditions and treatments and results in a single index score. Each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. EQ-5D index values range from -0.59 to 1.00. Higher EQ-5D Index scores represent better health status. The mITT analysis set includes all randomized subjects who received at least 1 dose of study agent and had at least 1 postbaseline efficacy assessment. Here, n indicates the number of subjects evaluated at specific timepoint for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 24, Week 48 and Early Termination

End point values	Epoetin Alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	45		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Index Score: Baseline (n= 75, 38)	0.709 (± 0.2678)	0.752 (± 0.2638)		
Index Score:Change baseline to Week 24 (n= 66, 34)	0.022 (± 0.3146)	0.042 (± 0.2779)		
Index Score:Change baseline to Week 48 (n= 29, 0)	0.032 (± 0.1658)	999 (± 999)		
IndexScore:Change baseline to Early Term.(n= 15,5)	0.011 (± 0.264)	0.01 (± 0.3402)		

Statistical analyses

Statistical analysis title	Statistical analysis -Index Score
Comparison groups	Epoetin Alfa v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon 2-sample test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 48

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Epoetin Alfa
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Reporting group description:

Subjects received a Starting dose of 450 International Unit per kilogram (IU/kg) of Epoetin Alfa (maximum total dose of 40,000 IU) administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (non-responders) and] and up to Week 48 for subjects who have entered in study extension phase.

Reporting group title	Placebo
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Reporting group description:

Subjects received a Starting dose of a matching volume of placebo were administered subcutaneously once every week during treatment phase [up to week 24 when no Erythroid response in subjects (nonresponders) and] and up to Week 48 for subjects who have entered in study extension phase.

Serious adverse events	Epoetin Alfa	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 85 (41.18%)	10 / 45 (22.22%)	
number of deaths (all causes)	7	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Myeloid Leukaemia			
subjects affected / exposed	2 / 85 (2.35%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Leukaemia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic Syndrome			
subjects affected / exposed	5 / 85 (5.88%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostate Cancer			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory Anaemia with An Excess of Blasts			
subjects affected / exposed	1 / 85 (1.18%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Dissection			
subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal Arteritis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee Arthroplasty			
subjects affected / exposed	2 / 85 (2.35%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			

subjects affected / exposed	4 / 85 (4.71%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Impaired Healing			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 85 (2.35%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	2 / 85 (2.35%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Social circumstances			
Elderly			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Anti-Erythropoietin Antibody Positive			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin Decreased			
subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip Fracture			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Brain Injury			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			

subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Age-Related Macular Degeneration			
subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoiditis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Neuropathic Ulcer			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Musculoskeletal and connective tissue disorders			
Intervertebral Disc Compression			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic Gangrene			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 85 (2.35%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth Abscess			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 85 (1.18%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Epoetin Alfa	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 85 (60.00%)	25 / 45 (55.56%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 85 (3.53%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 85 (7.06%)	5 / 45 (11.11%)	
occurrences (all)	7	25	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 85 (14.12%)	5 / 45 (11.11%)	
occurrences (all)	25	7	
Fatigue			
subjects affected / exposed	10 / 85 (11.76%)	3 / 45 (6.67%)	
occurrences (all)	13	3	
Oedema Peripheral			
subjects affected / exposed	4 / 85 (4.71%)	5 / 45 (11.11%)	
occurrences (all)	4	5	
Pyrexia			
subjects affected / exposed	7 / 85 (8.24%)	4 / 45 (8.89%)	
occurrences (all)	10	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 85 (4.71%)	3 / 45 (6.67%)	
occurrences (all)	5	3	
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	5 / 85 (5.88%)	2 / 45 (4.44%)	
occurrences (all)	6	2	
Constipation			
subjects affected / exposed	8 / 85 (9.41%)	0 / 45 (0.00%)	
occurrences (all)	9	0	
Diarrhoea			
subjects affected / exposed	9 / 85 (10.59%)	3 / 45 (6.67%)	
occurrences (all)	13	3	
Nausea			
subjects affected / exposed	6 / 85 (7.06%)	0 / 45 (0.00%)	
occurrences (all)	7	0	
Vomiting			
subjects affected / exposed	5 / 85 (5.88%)	1 / 45 (2.22%)	
occurrences (all)	5	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 85 (4.71%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Dyspnoea			
subjects affected / exposed	10 / 85 (11.76%)	1 / 45 (2.22%)	
occurrences (all)	15	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 85 (5.88%)	1 / 45 (2.22%)	
occurrences (all)	6	1	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 85 (3.53%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Bone Pain			
subjects affected / exposed	6 / 85 (7.06%)	0 / 45 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	7 / 85 (8.24%)	2 / 45 (4.44%)	
occurrences (all)	12	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2012	The second amendment (INT-2) was considered substantial and included specification that for all non-responders at Week 24, the treatment code would be broken after the Week 28 assessments. For responders at Week 48, the treatment code would be broken after Week 48, following assessment of response. It was also clarified that blinded study treatment would be administered to all subjects at Week 24, and that blood samples for erythropoietin antibody testing in Week 24 non-responders would be obtained after Week 24 response assessments. Additionally, study inclusion criterion 4 was modified: a maximum hemoglobin concentration of 10.5 gram per deciliter (g/dL) at baseline was deemed acceptable for subjects undergoing Red blood cells (RBC) transfusion between screening and baseline. For inclusion criterion 6, a transfusion requirement of less than or equal to ($\leq$) 4 RBC units over the 8 weeks before randomization was defined.
24 January 2013	The third amendment (INT-3; 24 January 2013) was considered substantial and included a number of changes to the inclusion/exclusion criteria to reduce the burden on subjects and to provide clarifications. Inclusion criteria 2 and 3 were modified to include diagnosis of myelodysplastic syndromes (MDS) and documentation of International Prognostic Scoring System (IPSS) during the screening phase as well as within the 12 weeks previously, but in case of signs of possible disease progression, a bone marrow aspirate/biopsy for diagnosis of primary MDS and an IPSS score were to be obtained during the screening period. In addition, the possibilities for retesting or rescreening were extended for potential subjects who were suitable for the study but temporarily ineligible due to either factors at screening that could be corrected or that were potentially due to fluctuations in laboratory tests. Inclusion criterion 5 was amended to clarify that erythropoietin could be retested. Additional changes allowed the resupply of vitamin B12 and/or folate to potential subjects who had confirmed MDS diagnosis but had B12/folate deficiency at screening. Such subjects could be eligible for study if adequate retested B12/folate levels were demonstrable before randomization. Inclusion criterion 4 was modified further such that the maximum allowable hemoglobin concentration of 10.5 g/dL was also applied to potential subjects who had received RBC transfusions within 2 weeks before screening. Changes to exclusion criteria included clarifications regarding: prior use of approved or experimental agents for the treatment of MDS ; history of uncontrolled hypertension; androgen or corticosteroid use; 2-week period before screening for prior treatment for neutropenia; and history of heart disease before screening. A new criterion was added to exclude patients who were receiving iron chelation therapy for greater than or equal ($\geq$) 6 months at screening for iron overload caused by blood transfusion.
19 February 2013	The local Country-specific protocol amendments that were considered were implemented in Germany (12th Feb 2013), Bulgaria (19th Feb 2014), and Greece (15th Feb 2013). The amendments provided an optional open-label treatment phase and were implemented in Germany, Bulgaria, and Greece. Non-responders at Week 24 who received placebo in the double-blind phase and responders at Week 48 who received epoetin alfa in the treatment extension phase could receive open-label epoetin alfa for up to 6 months after the end of the main double-blind study phase (Germany and Greece) or until up to 1 year after the last subject had enrolled in the open-label treatment phase (Bulgaria). The key aspects and results of the open-label treatment phase will be reported separately. Additionally, a local protocol amendment indicated that measurement of iron-binding capacity was optional in Germany, consistent with local clinical practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported