



Clinical trial results:

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)

Summary

EudraCT number	2009-016522-14
Trial protocol	CZ ES BE GR DE IT AT
Global end of trial date	14 September 2017

Results information

Result version number	v1 (current)
This version publication date	30 September 2018
First version publication date	30 September 2018

Trial information

Trial identification

Sponsor protocol code	20090160
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01362140
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	14 September 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the superiority of darbepoetin alfa versus placebo on the incidence of red blood cell transfusions during the 24-week double-blind treatment period in anemic patients with low or intermediate-1 risk MDS.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	147
EEA total number of subjects	143

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)	26
From 65 to 84 years	113
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 49 centers in 9 countries. Participants were enrolled from 21 December 2011 to 06 January 2014.

Pre-assignment

Screening details:

Eligible participants were randomized in a 2:1 ratio to receive darbepoetin alfa or placebo. Randomization was stratified by International Prognostic Scoring System (IPSS) category (low vs intermediate-1 risk) established at screening.

Period 1

Period 1 title	Double-blind Treatment 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	Placebo

Arm description:

Participants received placebo subcutaneous injection every 3 weeks (Q3W) for 24 weeks.

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:

Administered by subcutaneous injection every 3 weeks

Arm title	Darbepoetin alfa
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Arm description:

Participants received darbepoetin alfa 500 µg Q3W for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection every 3 weeks

Number of subjects in period 1	Placebo	Darbepoetin alfa
Started	49	98
Received Treatment	49	97
Completed	39	87
Not completed	10	11
Consent withdrawn by subject	3	3
Discontinued Without Receiving Treatment	-	1
Adverse event, non-fatal	2	2
Death	2	1
Other	1	1
Administrative Decision	-	1
Protocol-specified Criteria	1	2
Noncompliance	1	-

Period 2

Period 2 title	Active Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Darbepoetin alfa

Arm description:

During the active treatment period (starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks. Participants with a hemoglobin increase of < 1.5 g/dL relative to the start of darbepoetin alfa treatment in the absence of RBC transfusion in the previous 28 days could undergo dose escalation to 500 µg once every 2 weeks (Q2W) from week 31 onwards.

Arm type	Experimental
Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection every 3 weeks

Arm title	Darbepoetin alfa/Darbepoetin alfa
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Arm description:

During the active treatment period (starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks. Participants with a hemoglobin increase of < 1.5 g/dL relative to the start of darbepoetin alfa treatment in the absence of RBC transfusion in the previous 28 days could undergo dose escalation to 500 µg once every 2 weeks (Q2W) from week 31 onwards.

Arm type	Experimental
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Investigational medicinal product name	Darbepoetin alfa
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection every 3 weeks

Number of subjects in period 2	Placebo/Darbepoetin alfa	Darbepoetin alfa/Darbepoetin alfa
Started	39	87
Received Treatment	39	86
Completed	37	80
Not completed	2	7
Consent withdrawn by subject	1	3
Discontinued Without Receiving Treatment	-	1
Death	1	1
Other	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneous injection every 3 weeks (Q3W) for 24 weeks.	
Reporting group title	Darbepoetin alfa
Reporting group description:	
Participants received darbepoetin alfa 500 µg Q3W for 24 weeks.	

Reporting group values	Placebo	Darbepoetin alfa	Total
Number of subjects	49	98	147
Age categorical			
Units: Subjects			
Adults (18-64 years)	10	16	26
From 65-84 years	34	79	113
85 years and over	5	3	8
Age Continuous			
Units: years			
arithmetic mean	72.4	72.2	
standard deviation	± 9.3	± 9.5	-
Sex: Female, Male			
Units: Subjects			
Female	20	46	66
Male	29	52	81
IPSS Risk Category			
The Myelodysplastic Syndrome (MDS) IPSS score assesses the severity of MDS based on 3 prognostic factors each assigned a score: the percentage of bone marrow blasts, chromosome changes in the marrow cells (karyotype) and the presence of one or more low blood cell counts (cytopenias). The IPSS score is the sum of the bone marrow blast + karyotype + cytopenia score and ranges from 0 (low risk) to 3.5 (high risk). Prognosis is categorized as Low risk (score = 0), Intermediate-1 (score 0.5 to 1.0), Intermediate-2 (score 1.5 to 2.0) or High risk (score ≥ 2.5).			
Units: Subjects			
Low	25	50	75
Intermediate-1	24	48	72
Race/Ethnicity, Customized			
Units: Subjects			
White	49	98	147
Ethnicity (NIH/OMB)			
French clinical sites, per regulation, did not complete the ethnicity question.			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	45	91	136
Unknown or Not Reported	3	5	8
World Health Organization (WHO) Classification of MDS			
The World Health Organization (WHO) classification recognizes eight subtypes of MDS that are distinguished by the percentage of myeloblasts, presence or absence of ringed sideroblasts (i.e., erythroid precursors with iron deposits surrounding the nucleus), presence of a monocytosis or a deletion 5q.			
Units: Subjects			

Refractory anemia (RA)	13	10	23
RA with ringed sideroblasts (RARS)	4	17	21
Refractory cytopenia multilineage dysplasia (RCMD)	19	45	64
MDS, unclassified (MDS-U)	1	1	2
MDS associated with isolated del (5q)	2	11	13
Refractory anemia with excess blasts-1 (RAEB-1)	10	13	23
Refractory anemia with excess blasts-2 (RAEB-2)	0	0	0
Unknown	0	1	1
Time since MDS Diagnosis			
Data available for 43 and 89 participants in each treatment group respectively			
Units: months			
arithmetic mean	11.7	12.5	
standard deviation	± 17.6	± 16.6	-
Hemoglobin			
Data available for 35 and 75 participants in each treatment group respectively			
Units: g/dL			
arithmetic mean	9.10	9.23	
standard deviation	± 0.87	± 0.70	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received placebo subcutaneous injection every 3 weeks (Q3W) for 24 weeks.	
Reporting group title	Darbepoetin alfa
Reporting group description: Participants received darbepoetin alfa 500 µg Q3W for 24 weeks.	
Reporting group title	Placebo/Darbepoetin alfa
Reporting group description: During the active treatment period (starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks. Participants with a hemoglobin increase of < 1.5 g/dL relative to the start of darbepoetin alfa treatment in the absence of RBC transfusion in the previous 28 days could undergo dose escalation to 500 µg once every 2 weeks (Q2W) from week 31 onwards.	
Reporting group title	Darbepoetin alfa/Darbepoetin alfa
Reporting group description: During the active treatment period (starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks. Participants with a hemoglobin increase of < 1.5 g/dL relative to the start of darbepoetin alfa treatment in the absence of RBC transfusion in the previous 28 days could undergo dose escalation to 500 µg once every 2 weeks (Q2W) from week 31 onwards.	
Subject analysis set title	LTFU: Placebo/Darbepoetin alfa
Subject analysis set type	Safety analysis
Subject analysis set description: Participants who received placebo in the double-blind treatment period and darbepoetin alfa in the active treatment period then entered the long-term follow-up period (LTFU).	
Subject analysis set title	LTFU: Darbepoetin alfa/Darbepoetin alfa
Subject analysis set type	Safety analysis
Subject analysis set description: Participants who received darbepoetin alfa in the double-blind treatment period and darbepoetin alfa in the active treatment period then entered the long-term follow-up period.	

Primary: Percentage of Participants with at Least One Red Blood Cell (RBC) Transfusion During the Double-blind Treatment Period

End point title	Percentage of Participants with at Least One Red Blood Cell (RBC) Transfusion During the Double-blind Treatment Period
End point description: This endpoint was analyzed in the Transfusion Primary Analysis Set which includes all randomized and consented participants who received at least 1 dose of study drug and who had an end of treatment period (EOTP) visit ≥ day 29 (ie, start of week 5).	
End point type	Primary
End point timeframe: Week 5 to Week 25	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	97		
Units: percentage of participants				
number (not applicable)	59.2	36.1		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: The primary hypothesis to be tested was that the percentage of participants with at least 1 RBC transfusion from week 5 to the EOTP was lower in the darbepoetin alfa group than in the placebo group. This hypothesis was confirmed if the incidence of RBC transfusion in the darbepoetin alfa group was lower and had a p-value < 0.05 from a 2-sided Chi-square test.	
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Chi-squared

Secondary: Percentage of Participants Who Achieved an Erythroid Response Based on International Working Group (IWG) 2006 Criteria in the Double-blind Treatment Period

End point title	Percentage of Participants Who Achieved an Erythroid Response Based on International Working Group (IWG) 2006 Criteria in the Double-blind Treatment Period
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End point description:

International Working Group 2006 erythroid response was defined as 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. Participants with no hemoglobin collected to the minimum time required to observe an IWG erythroid response (Week 13) were considered non-responders.

The analysis was conducted in primary analysis set participants (all randomized and consented participants who received at least 1 dose of investigational product) with a central laboratory baseline hemoglobin value.

End point type	Secondary
End point timeframe: Up to 24 weeks	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	75		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.00 to 10.00)	14.7 (7.56 to 24.73)		

Statistical analyses

Statistical analysis title	Treatment Difference
Statistical analysis description:	
If the primary hypothesis was confirmed, the secondary hypothesis to be tested was that the percentage of participants achieving an IWG erythroid response during the 24-week double-blind treatment period was greater in the darbepoetin alfa group than in the placebo group. This hypothesis was confirmed if erythroid response was higher in the darbepoetin alfa group and the p-value was < 0.05 from a 2-sided Cochran-Mantel-Haenszel test using the IPSS as a stratification factor.	
Comparison groups	Placebo v Darbepoetin alfa
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 ^[1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The overall 2-sided CMH test with IPSS score as stratification factor.

Secondary: Number of Participants with Adverse Events During the Double-blind Treatment Period

End point title	Number of Participants with Adverse Events During the Double-blind Treatment Period
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End point description:

The severity of each adverse event was graded using the the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading scale, where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening and grade 5 = death. Prespecified adverse events of interest for darbepoetin alfa, based on clinical data in anemic patients with cancer, included the following categories: hypersensitivity, cardiac failure, hypertension, malignancies, embolic and thrombotic events, venous thromboembolic events (VTEs), central nervous system vascular disorders, and ischemic heart disease.

This endpoint was analyzed in the Safety Analysis Set, which includes all participants who received at least 1 dose of study drug. One participant in the placebo arm inadvertently received a dose of darbepoetin alfa and is included in the darbepoetin alfa group for safety analyses.

End point type	Secondary
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End point timeframe:

From first dose of study drug until the end of the double-blind treatment period; 24 weeks for participants who proceeded into the active treatment period and up to 26 weeks for participants who did not enter the active treatment period.

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	98		
Units: participants				
Any adverse event (AE)	37	80		
AE Grade ≥ 2	23	42		
AE Grade ≥ 3	13	15		
AE Grade ≥ 4	6	5		
Serious adverse events (SAE)	8	11		
AE leading to discontinuation of study drug	2	3		
Fatal adverse events	2	1		
Adverse events of special interest	13	16		

Treatment-related adverse events (TRAE)	4	5		
Treatment-related serious adverse events	0	1		
TRAE leading to discontinuation of study drug	0	1		
Treatment-related fatal adverse events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events During the Active Treatment Period

End point title	Number of Participants with Adverse Events During the Active Treatment Period
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End point description:

The severity of each adverse event was graded using the the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading scale, where grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening and grade 5 = death. Prespecified adverse events of interest for darbepoetin alfa, based on clinical data in anemic patients with cancer, included the following categories: hypersensitivity, cardiac failure, hypertension, malignancies, embolic and thrombotic events, venous thromboembolic events (VTEs), central nervous system vascular disorders, and ischemic heart disease.

This endpoint was analyzed in participants who received at least 1 dose of darbepoetin alfa in the active treatment period. One participant originally randomized to placebo inadvertently received a dose of darbepoetin alfa during the double-blind treatment period and was included in the darbepoetin/darbepoetin group for all safety analysis.

End point type	Secondary
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End point timeframe:

From first dose of treatment in the active treatment period (week 25) to 30 days after last dose; up to 51 weeks.

End point values	Placebo/Darbepoetin alfa	Darbepoetin alfa/Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	87		
Units: participants				
Any adverse event (AE)	32	74		
AE Grade $\geq$ 2	25	52		
AE Grade $\geq$ 3	9	27		
AE Grade $\geq$ 4	4	9		
Serious adverse events (SAE)	7	22		
AE leading to discontinuation of study drug	3	3		
Fatal adverse events	1	1		
Adverse events of special interest	8	20		
Treatment-related adverse events (TRAE)	3	6		
Treatment-related serious adverse events	1	1		

TRAE leading to discontinuation of study drug	1	0		
Treatment-related fatal adverse events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease Progression to Acute Myeloid Leukemia (AML) in the Double-blind Treatment Period

End point title	Number of Participants with Disease Progression to Acute Myeloid Leukemia (AML) in the Double-blind Treatment Period
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End point description:

Transformation to AML was assessed according to WHO guidelines in the absence of IP and any haematopoietic growth factors (2 weeks off dosing). Bone marrow and/or cytogenetic report confirmation of AML was required (marrow or peripheral blast cells $\geq$ 20%, presence of pathognomic AML cytogenetic change, or evidence of marrow blast criteria for erythroleukemia). A pathology report confirming other leukemias such as chloroma (granulocytic sarcoma, myeloid sarcoma) or leukemia cutis also constituted transformation to AML.

This endpoint was analyzed in the safety analysis set with available data.

End point type	Secondary
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End point timeframe:

24 weeks

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	95		
Units: participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease Progression to AML in the Active Treatment Period

End point title	Number of Participants with Disease Progression to AML in the Active Treatment Period
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End point description:

Transformation to AML was assessed according to WHO guidelines in the absence of IP and any haematopoietic growth factors (2 weeks off dosing). Bone marrow and/or cytogenetic report confirmation of AML was required (marrow or peripheral blast cells $\geq$ 20%, presence of pathognomic AML cytogenetic change, or evidence of marrow blast criteria for erythroleukemia). A pathology report confirming other leukemias such as chloroma (granulocytic sarcoma, myeloid sarcoma) or leukemia cutis also constituted transformation to AML.

This endpoint was analyzed in all participants who received at least one dose of darbepoetin alfa in the active treatment period with available AML data.

End point type	Secondary
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End point timeframe:

Week 26 to week 73

End point values	Placebo/Darbepoetin alfa	Darbepoetin alfa/Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	87		
Units: participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease Progression to Acute Myeloid Leukemia (AML) in the Long-term Follow-up Period

End point title	Number of Participants with Disease Progression to Acute Myeloid Leukemia (AML) in the Long-term Follow-up Period
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End point description:

Transformation to AML was assessed according to WHO guidelines in the absence of IP and any haematopoietic growth factors (2 weeks off dosing). Bone marrow and/or cytogenetic report confirmation of AML was required (marrow or peripheral blast cells $\geq 20\%$, presence of pathognomic AML cytogenetic change, or evidence of marrow blast criteria for erythroleukemia). A pathology report confirming other leukemias such as chloroma (granulocytic sarcoma, myeloid sarcoma) or leukemia cutis also constituted transformation to AML.

This endpoint was analyzed in all participants who entered the long-term follow-up period.

End point type	Secondary
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End point timeframe:

Week 72 until end of study (14 September 2017), a maximum of 138 weeks.

End point values	LTFU: Placebo/Darbepoetin alfa	LTFU: Darbepoetin alfa/Darbepoetin alfa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	88		
Units: participants	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Malignancies Other Than AML, Basal Cell Carcinoma, or Squamous Cell Carcinoma of the Skin

End point title	Number of Participants with Malignancies Other Than AML,
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End point description:

End point type Secondary

End point timeframe:

Up to 24 weeks

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	98		
Units: participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Neutralizing Antibodies to Darbepoetin Alfa

End point title Number of Participants who Developed Neutralizing Antibodies to Darbepoetin Alfa

End point description:

Two validated assays were used to detect the presence of anti-darbepoetin alfa antibodies. Samples were first tested in an immunoassay to detect antibodies capable of binding to darbepoetin alfa. Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based assay to determine neutralizing activity against darbepoetin alfa. 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 number of participants who developed antibodies to darbepoetin alfa is defined as participants who were neutralizing antibody positive post-baseline with a negative or no result at baseline.

This endpoint was analyzed in the safety analysis set participants with post-baseline antibody results.

End point type Secondary

End point timeframe:

Baseline to end of active treatment period (73 weeks)

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	93		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
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End point description:

The FACIT-Fatigue scale was a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The FACIT-Fatigue scale score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. A positive change from baseline score indicates an improvement. End of double-blind treatment period (EOTP) and end of active treatment period (EOATP) analyses includes last available values.

This endpoint was analyzed in the FACIT-Fatigue Analysis Set, which includes all participants in the primary analysis set who completed or partially completed both the baseline and at least 1 subsequent FACIT-F questionnaire.

End point type	Secondary
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End point timeframe:

Baseline, and weeks 13, 25, 31, 42/43, 54/55, and 72/73

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	90		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 42, 90)	32.9 (± 11.4)	33.1 (± 11.4)		
Change from Baseline to Week 13 (n = 41, 85)	-0.9 (± 9.0)	2.7 (± 7.2)		
Change from Baseline to Week 25 (n = 39, 85)	0.6 (± 5.5)	1.2 (± 8.9)		
Change from Baseline to EOTP (n = 42, 90)	-0.5 (± 7.1)	1.1 (± 8.8)		
Change from baseline to week 31 (n = 36, 78)	2.7 (± 8.3)	1.6 (± 8.9)		
Change from baseline to week 42/43 (n = 29, 77)	1.9 (± 9.0)	1.8 (± 8.4)		
Change from baseline to week 54/55 (n = 31, 67)	2.6 (± 11.4)	1.3 (± 9.1)		
Change from baseline to week 72/73 (n = 23, 60)	2.3 (± 10.6)	1.2 (± 12.2)		
Change from baseline to EOATP (n = 38, 87)	0.5 (± 10.7)	1.7 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5D (EQ-5D) Visual Analog Scale (VAS)

End point title	Change from Baseline in EuroQol-5D (EQ-5D) Visual Analog Scale (VAS)
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End point description:

The EQ-5D visual analog scale (VAS) is a global evaluation of overall health state with scores ranging from 0 (worse health state a participant can imagine) to 100 (best health state a participant can imagine). End of double-blind treatment period (EOTP) and end of active treatment period (EOATP)

analyses includes last available values.

This endpoint was analyzed in the EQ-5D visual analog analysis set which includes all participants in the primary analysis set who completed both the baseline and at least 1 subsequent visual analog scale.

End point type	Secondary
End point timeframe:	
Baseline, and weeks 13, 25, 31, 42/43, 54/55, and 72/73	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	90		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 42, 90)	64.4 (± 17.9)	64.8 (± 17.2)		
Change from Baseline to Week 13 (n = 41, 83)	-1.9 (± 15.5)	2.9 (± 13.0)		
Change from Baseline to Week 25 (n = 39, 81)	2.1 (± 15.3)	2.4 (± 13.5)		
Change from Baseline to EOTP (n = 42, 89)	0.8 (± 15.7)	2.1 (± 13.1)		
Change from baseline to week 31 (n = 36, 75)	3.4 (± 15.0)	1.9 (± 13.7)		
Change from baseline to week 42/43 (n = 29, 76)	4.7 (± 15.7)	4.4 (± 14.2)		
Change from baseline to week 54/55 (n = 30, 66)	4.2 (± 21.9)	2.1 (± 17.6)		
Change from baseline to week 72/73 (n = 23, 59)	5.7 (± 18.0)	2.3 (± 20.6)		
Change from baseline to EOATP (n = 38, 87)	1.2 (± 18.5)	2.3 (± 18.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Clinically Meaningful Improvement in Fatigue

End point title	Percentage of Participants with a Clinically Meaningful Improvement in Fatigue
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End point description:

The FACIT-Fatigue scale was a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The FACIT-Fatigue scale score ranges from 0 to 52, with higher scores denoting lower levels of fatigue. Clinically meaningful improvement in fatigue is defined as an increase of ≥ 3 points in the FACIT-Fatigue subscale score, from baseline.

This endpoint was analyzed in the FACIT-fatigue analysis set.

End point type	Secondary
End point timeframe:	
Baseline to week 24 (end of double-blind treatment period) and week 73 (end of active treatment period)	

End point values	Placebo	Darbepoetin alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	90		
Units: percentage of participants				
number (confidence interval 95%)				
End of double-blind treatment period	31.0 (17.62 to 47.09)	35.6 (25.74 to 46.35)		
End of active treatment period (n = 38, 87)	36.8 (21.81 to 54.01)	39.1 (28.79 to 50.13)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24-week double-blind treatment period and 48-week active treatment period. The long-term follow-up period includes deaths and adverse events that occurred after week 73 through week 156.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	DBTP: Placebo
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Reporting group description:

Participants received placebo subcutaneous injection every 3 weeks (Q3W) for 24 weeks in the double-blind treatment phase (DBTP).

Reporting group title	DBTP: Darbepoetin alfa
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Reporting group description:

Participants received darbepoetin alfa 500 µg Q3W for 24 weeks in the DBTP.

Reporting group title	ATP: Placebo
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Reporting group description:

During the active treatment period (ATP; starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks.

Reporting group title	ATP: Darbepoetin alfa
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Reporting group description:

During the active treatment period (starting at week 25), participants received darbepoetin alfa 500 µg Q3W for 48 weeks.

Reporting group title	LTFU: Placebo
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Reporting group description:

Long-term follow-up (LTFU) occurred from the end of treatment for a minimum of 3 years from the first dose of study drug.

Reporting group title	LTFU: Darbepoetin alfa
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Reporting group description:

Long-term follow-up (LTFU) occurred from the end of treatment for a minimum of 3 years from the first dose of study drug.

Serious adverse events	DBTP: Placebo	DBTP: Darbepoetin alfa	ATP: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 48 (16.67%)	11 / 98 (11.22%)	7 / 38 (18.42%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myelodysplastic syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent placement			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent occlusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Menorrhagia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinoatrial block			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Haemorrhage intracranial			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	3 / 98 (3.06%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Proctitis haemorrhagic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 48 (4.17%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess of salivary gland			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tetany			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ATP: Darbepoetin alfa	LTFU: Placebo	LTFU: Darbepoetin alfa
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 87 (25.29%)	7 / 40 (17.50%)	14 / 88 (15.91%)
number of deaths (all causes)	1	11	25
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myelodysplastic syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent placement			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent occlusion			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinoatrial block			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemorrhage intracranial			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 87 (2.30%)	1 / 40 (2.50%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 87 (1.15%)	2 / 40 (5.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Proctitis haemorrhagic			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Calculus bladder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			

subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess of salivary gland			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 40 (2.50%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pneumonia bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 87 (0.00%)	2 / 40 (5.00%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Soft tissue infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	0 / 87 (0.00%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tetany			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	DBTP: Placebo	DBTP: Darbepoetin alfa	ATP: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 48 (72.92%)	80 / 98 (81.63%)	32 / 38 (84.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Basal cell carcinoma subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Myelodysplastic syndrome subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Uterine leiomyoma subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Vascular disorders			
Aortic arteriosclerosis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Circulatory collapse subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Haematoma subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Hot flush subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Hypertensive crisis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Hypotension subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Intermittent claudication			

subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Varicose vein			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Vasculitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Vein disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia repair			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Tooth extraction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site bruise			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	5 / 48 (10.42%)	12 / 98 (12.24%)	5 / 38 (13.16%)
occurrences (all)	8	17	7
Chest discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Chest pain			

subjects affected / exposed	0 / 48 (0.00%)	3 / 98 (3.06%)	0 / 38 (0.00%)
occurrences (all)	0	4	0
Drug ineffective			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	4 / 48 (8.33%)	17 / 98 (17.35%)	0 / 38 (0.00%)
occurrences (all)	5	19	0
Gait disturbance			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	2 / 48 (4.17%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Hernia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	1	2	0
Injection site haematoma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	4 / 48 (8.33%)	3 / 98 (3.06%)	1 / 38 (2.63%)
occurrences (all)	4	3	1
Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	9 / 98 (9.18%) 13	1 / 38 (2.63%) 2
Swelling subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Temperature intolerance subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Menorrhagia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 98 (2.04%) 2	0 / 38 (0.00%) 0
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	4 / 98 (4.08%) 4	3 / 38 (7.89%) 3

Dysphonia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	2 / 48 (4.17%)	5 / 98 (5.10%)	0 / 38 (0.00%)
occurrences (all)	3	5	0
Dyspnoea exertional			
subjects affected / exposed	5 / 48 (10.42%)	6 / 98 (6.12%)	1 / 38 (2.63%)
occurrences (all)	6	9	1
Epistaxis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	3 / 38 (7.89%)
occurrences (all)	1	1	4
Hydrothorax			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Lung disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Pleural effusion			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Productive cough			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Pulmonary hypertension			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Pulmonary thrombosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Reflux laryngitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Rhonchi			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Sinus disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Agitated depression			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Insomnia			

subjects affected / exposed	3 / 48 (6.25%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	3	0	1
Nervousness			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blast cell count increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Body temperature increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Breath sounds abnormal			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	4	0
C-reactive protein increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Intraocular pressure test			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Serum ferritin increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	4 / 98 (4.08%) 5	1 / 38 (2.63%) 1
Weight increased subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Face injury subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Fall subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Joint injury subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	1 / 38 (2.63%) 1
Ligament rupture subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 98 (2.04%) 2	0 / 38 (0.00%) 0
Muscle strain			

subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Periorbital haematoma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Post procedural swelling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Rib fracture			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Scratch			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Spinal column injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Transfusion reaction			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			

subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Cardiac failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Extrasystoles			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 48 (0.00%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Sinus bradycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Tachyarrhythmia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Cerebrovascular accident			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Cognitive disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	3 / 48 (6.25%)	5 / 98 (5.10%)	2 / 38 (5.26%)
occurrences (all)	3	5	2
Dizziness postural			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Dysgeusia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 48 (2.08%)	7 / 98 (7.14%)	0 / 38 (0.00%)
occurrences (all)	1	8	0
Leukoencephalopathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Polyneuropathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Agranulocytosis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 98 (2.04%)	1 / 38 (2.63%)
occurrences (all)	2	3	1
Haemolysis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	4
Lymphadenopathy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	2 / 38 (5.26%)
occurrences (all)	4	4	3
Splenomegaly			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	1	3	0
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 48 (2.08%)	3 / 98 (3.06%)	1 / 38 (2.63%)
occurrences (all)	1	3	1
Eye disorders			
Asthenopia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	3
Conjunctival haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Dacryostenosis acquired			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Erythema of eyelid			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Eye disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Eye haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Glaucoma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Periorbital oedema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	0	4	0
Abdominal pain upper			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	1 / 38 (2.63%)
occurrences (all)	1	3	1
Anal haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	2 / 38 (5.26%)
occurrences (all)	1	2	2
Duodenal ulcer			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	1	2	0
Dysphagia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Enteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0

Enterocolitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Epigastric discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Gingival recession			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	2 / 48 (4.17%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Haemorrhoids			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hiatus hernia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Ileus paralytic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1

Inguinal hernia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Intestinal polyp			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Noninfective gingivitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Tongue ulceration			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Tooth socket haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Varices oesophageal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1

Vomiting subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Hepatobiliary disorders			
Biliary colic subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 2
Cholecystitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Cholelithiasis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	1 / 38 (2.63%) 1
Gallbladder polyp subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Hepatic cirrhosis subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Hepatosplenomegaly subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Portal hypertension subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Exfoliative rash			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 48 (0.00%)	2 / 98 (2.04%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	1 / 48 (2.08%)	3 / 98 (3.06%)	0 / 38 (0.00%)
occurrences (all)	2	4	0
Pruritus generalised			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	1 / 38 (2.63%)
occurrences (all)	1	2	1
Skin haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Crush syndrome subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Nocturia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Prerenal failure subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Renal cyst subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Renal disorder subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Renal pain subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Urethral prolapse subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Urethritis noninfective subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Endocrine disorders Hyperparathyroidism			

subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Thyroid mass			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 48 (6.25%)	6 / 98 (6.12%)	3 / 38 (7.89%)
occurrences (all)	4	6	4
Back pain			
subjects affected / exposed	2 / 48 (4.17%)	8 / 98 (8.16%)	3 / 38 (7.89%)
occurrences (all)	2	9	4
Bone pain			
subjects affected / exposed	2 / 48 (4.17%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	2	1	0
Chondritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Groin pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Haemarthrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Joint swelling			

subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Muscle rigidity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)	4 / 98 (4.08%)	3 / 38 (7.89%)
occurrences (all)	1	5	4
Muscular weakness			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	3 / 48 (6.25%)	0 / 98 (0.00%)	3 / 38 (7.89%)
occurrences (all)	3	0	3
Musculoskeletal stiffness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	5 / 98 (5.10%)	2 / 38 (5.26%)
occurrences (all)	0	5	4
Myofascial pain syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Osteoarthritis			

subjects affected / exposed	0 / 48 (0.00%)	3 / 98 (3.06%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Osteopenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	2 / 48 (4.17%)	2 / 98 (2.04%)	2 / 38 (5.26%)
occurrences (all)	2	2	2
Polymyalgia rheumatica			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	2 / 48 (4.17%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	2	1	1
Bronchitis viral			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0

Dacryocystitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Device related infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Epididymitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	2 / 38 (5.26%)
occurrences (all)	1	0	2
Gastroenteritis viral			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Laryngitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Localised infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1

Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Lung infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Onychomycosis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Oral fungal infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 98 (2.04%) 2	1 / 38 (2.63%) 1
Oropharyngeal candidiasis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Otitis externa subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Paronychia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 2	0 / 38 (0.00%) 0
Periodontitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	0 / 38 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	2 / 98 (2.04%) 2	0 / 38 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1

Respiratory moniliasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	3 / 98 (3.06%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Skin bacterial infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 98 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 98 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 48 (4.17%)	2 / 98 (2.04%)	1 / 38 (2.63%)
occurrences (all)	2	2	1
Urinary tract infection bacterial			
subjects affected / exposed	0 / 48 (0.00%)	1 / 98 (1.02%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	1 / 48 (2.08%)	2 / 98 (2.04%)	1 / 38 (2.63%)
occurrences (all)	1	2	1

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	8 / 98 (8.16%) 8	6 / 38 (15.79%) 7
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	3 / 98 (3.06%) 3	0 / 38 (0.00%) 0
Fluid overload subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 2	1 / 98 (1.02%) 1	1 / 38 (2.63%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 98 (0.00%) 0	0 / 38 (0.00%) 0
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 98 (0.00%) 0	1 / 38 (2.63%) 1
Iron overload subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 98 (1.02%) 1	1 / 38 (2.63%) 1

Non-serious adverse events	ATP: Darbepoetin alfa	LTFU: Placebo	LTFU: Darbepoetin alfa
Total subjects affected by non-serious adverse events subjects affected / exposed	73 / 87 (83.91%)	1 / 40 (2.50%)	1 / 88 (1.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Basal cell carcinoma subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0

Myelodysplastic syndrome subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Uterine leiomyoma subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Vascular disorders			
Aortic arteriosclerosis subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Circulatory collapse subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Deep vein thrombosis subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Haematoma subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Hot flush subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	1 / 40 (2.50%) 1	0 / 88 (0.00%) 0
Hypertensive crisis subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Intermittent claudication subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Varicose vein			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Vasculitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Vein disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Inguinal hernia repair			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Tooth extraction			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Application site bruise			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	10 / 87 (11.49%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	21	0	0
Chest discomfort			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Drug ineffective			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	12 / 87 (13.79%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	14	0	0
Gait disturbance			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hernia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Injection site haematoma			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	6	0	0
Pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Peripheral swelling			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Pyrexia			

subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 8	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Swelling subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Temperature intolerance subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Menorrhagia subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 5	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0

Dyspnoea			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	9	0	0
Dyspnoea exertional			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Hydrothorax			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Lung disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Pulmonary hypertension			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Pulmonary thrombosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Reflux laryngitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Rhinorrhoea			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Rhonchi			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Sinus disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitated depression			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Delirium			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Nervousness			

subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Investigations			
Blast cell count increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Blood urea increased subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Body temperature increased subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Breath sounds abnormal subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Intraocular pressure test subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 2	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 3	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Serum ferritin increased subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0

Weight decreased subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 10	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 3	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Face injury subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Ligament rupture subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Muscle strain subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 40 (0.00%) 0	0 / 88 (0.00%) 0
Periorbital haematoma			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Post procedural swelling			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Spinal column injury			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Transfusion reaction			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			

subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Extrasystoles			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Sinus bradycardia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Tachyarrhythmia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cerebrovascular accident			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	6	0	0
Dizziness postural			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	6 / 87 (6.90%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	8	0	0
Leukoencephalopathy			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Migraine			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Polyneuropathy			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	6	0	0
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Anaemia			

subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	22	0	0
Haemolysis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	7	0	0
Splenomegaly			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	6	0	0
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Blepharitis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Dacryostenosis acquired			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Erythema of eyelid			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Eye disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Eye haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Glaucoma			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0

Abdominal pain			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Abdominal pain upper			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	5	0	0
Anal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	7	0	0
Diarrhoea			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	5	0	0
Duodenal ulcer			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Dysphagia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Enteritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0

Epigastric discomfort			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Gingival recession			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	2 / 87 (2.30%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences (all)	2	1	0
Hiatus hernia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Ileus paralytic			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Intestinal polyp			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	7	0	0
Noninfective gingivitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Odynophagia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Tongue ulceration			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Tooth socket haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Varices oesophageal			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	5	0	0

Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cholecystitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Cholelithiasis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Gallbladder polyp			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hepatic cirrhosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hepatosplenomegaly			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Portal hypertension			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Exfoliative rash			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Pruritus generalised			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 87 (1.15%)	1 / 40 (2.50%)	0 / 88 (0.00%)
occurrences (all)	1	1	0
Skin haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Chronic kidney disease			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Crush syndrome			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Haematuria			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Prerenal failure			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Renal disorder			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Renal pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Urethral prolapse			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Urethritis noninfective			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Thyroid mass			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	7	0	0
Back pain			
subjects affected / exposed	5 / 87 (5.75%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	6	0	0
Bone pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Chondritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Haemarthrosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc disorder			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Limb discomfort			

subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Muscle rigidity			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Myofascial pain syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Osteopenia			

subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Polymyalgia rheumatica			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Bronchitis viral			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Cystitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Dacryocystitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Device related infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Epididymitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0

Lung infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Oral fungal infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Oral herpes			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Respiratory moniliasis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0

Respiratory tract infection			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Respiratory tract infection viral			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Sepsis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Skin bacterial infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	4	0	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	2 / 87 (2.30%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	2	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 87 (6.90%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	7	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0
Fluid overload			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	4 / 87 (4.60%)	0 / 40 (0.00%)	1 / 88 (1.14%)
occurrences (all)	5	0	1
Hypokalaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Iron overload			
subjects affected / exposed	3 / 87 (3.45%)	0 / 40 (0.00%)	0 / 88 (0.00%)
occurrences (all)	3	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2012	- 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
25 September 2013	- 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
07 April 2014	- 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
10 August 2015	- 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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.

Notes: