Clinical trial results:
A PHASE 3, DOUBLE-BLIND, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO FOR THE TREATMENT OF ANEMIA DUE TO IPSS-R VERY LOW, LOW, OR INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES IN SUBJECTS WITH RING SIDEROBLASTS WHO REQUIRE RED BLOOD CELL TRANSFUSIONS

Summary

EudraCT number	2015-003454-41
Trial protocol	DE ES NL BE SE IT
Global end of trial date	26 November 2020

Results information

Result version number	v1
This version publication date	05 December 2021
First version publication date	05 December 2021

Trial information

Trial identification

Sponsor protocol code	ACE-536-MDS-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	22 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate RBC transfusion independence (RBC-TI) of luspatercept compared with placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require red blood cell (RBC) transfusions.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	229
EEA total number of subjects	148

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)	45
From 65 to 84 years	174
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

229 participants were randomized and treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Luspatercept

Arm description:

Luspatercept 1.0 mg/Kg SC on Day 1 of each 21-day treatment cycle

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	ACE-536
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.0 mg/kg subcutaneously injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle)

Arm title	Placebo

Arm description:

Placebo (Volume equivalent to experimental arm) SC on Day 1 of each 21-day treatment cycle

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

Dosage and administration details:

Volume equivalent to experimental arm, subcutaneously injection every 3 weeks

Number of subjects in period 1	Luspatercept	Placebo
Started	153	76
Completed	4	12
Not completed	149	64
Adverse event, serious fatal	45	24

Consent withdrawn by subject	35	13
Other reasons	12	5
Lost to follow-up	5	1
Transition to rollover protocol	52	21

Baseline characteristics

Reporting groups	
Reporting group title	Luspatercept
Reporting group description:	
Luspatercept 1.0 mg/Kg SC on Day 1 of each 21-day treatment cycle	
Reporting group title	Placebo
Reporting group description:	
Placebo (Volume equivalent to experimental arm) SC on Day 1 of each 21-day treatment cycle	

Reporting group values	Luspatercept	Placebo	Total
Number of subjects	153	76	229
Age categorical Units: Subjects			
Adults (18-64 years)	29	16	45
From 65-84 years	120	54	174
85 years and over	4	6	10
Age Continuous Units: Years			
arithmetic mean	70.5	70.7	
standard deviation	± 8.68	± 10.88	-
Sex: Female, Male Units: Participants			
Female	59	26	85
Male	94	50	144
Race/Ethnicity, Customized Units: Subjects			
Black or African American	1	0	1
White	107	51	158
Not Collected or Reported	44	24	68
Other	1	1	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	4	7
Not Hispanic or Latino	115	52	167
Unknown or Not Reported	35	20	55

End points

End points reporting groups

Reporting group title	Luspatercept
Reporting group description:	
Luspatercept 1.0 mg/Kg SC on Day 1 of each 21-day treatment cycle	
Reporting group title	Placebo
Reporting group description:	
Placebo (Volume equivalent to experimental arm) SC on Day 1 of each 21-day treatment cycle	

Primary: Percentage Of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 Weeks From Week 1 to Week 24

End point title	Percentage Of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 Weeks From Week 1 to Week 24
End point description:	
RBC-TI response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 56-day (8-week) period (ie, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc.) during the first 24 weeks of study treatment. Participants had to have at least 56 days (≥ 8 weeks) of transfusion independence prior to (and including) the Week 24 cut-off date to qualify as a responder. Participants who failed to achieve RBC-TI at least 56 days prior to or on the cut-off date were counted as non-responders.	
End point type	Primary
End point timeframe:	
From Week 1 through Week 24 of study treatment	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percent of Participants				
number (confidence interval 95%)	37.91 (30.20 to 46.10)	13.16 (6.49 to 22.87)		

Statistical analyses

Statistical analysis title	RBC-TI ≥ 8 weeks_1
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Risk Difference on Response Rate
Point estimate	24.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	14.48
upper limit	34.64

Statistical analysis title	RBC-TI ≥ 8 weeks_2
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.278
upper limit	11.259

Secondary: Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 12 Weeks From Week 1 to Week 24

End point title	Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 12 Weeks From Week 1 to Week 24

End point description:

RBC-TI Response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 24 weeks of treatment.

End point type	Secondary

End point timeframe:

From Week 1 through Week 24 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percent of Participants				
number (confidence interval 95%)	28.10 (21.14 to 35.93)	7.89 (2.95 to 16.40)		

Statistical analyses

Statistical analysis title	RBC-TI ≥ 12 weeks_1
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Risk Difference on Response Rate
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.92
upper limit	29.08

Statistical analysis title	RBC-TI ≥ 12 weeks_2
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.002
upper limit	12.844

Secondary: Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 12 Weeks From Week 1 to Week 48

End point title	Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 12 Weeks From Week 1 to Week 48

End point description:

RBC-TI Response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 48 weeks of treatment.

End point type	Secondary

End point timeframe:

From Week 1 through Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percent of Participants				
number (confidence interval 95%)	33.33 (25.93 to 41.40)	11.84 (5.56 to 21.29)		

Statistical analyses

Statistical analysis title	RBC-TI ≥ 12 weeks_3
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Risk Difference on Response Rate
Point estimate	21.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.23
upper limit	31.51

Statistical analysis title	RBC-TI ≥ 12 weeks_4
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.827
upper limit	8.956

Secondary: Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 Weeks From Week 1 Through Week 48

End point title	Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) ≥ 8 Weeks From Week 1 Through Week 48

End point description:

RBC-TI response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 56-day (8-week) period (ie, Days 1 to 56, Days 2 to 57, Days 3 to 58, etc.) during Week 1 through Week 48. Participants had to have at least 56 days (≥ 8 weeks) of transfusion independence prior to (and including) the Week 48 cut-off date to qualify as a responder. Participants who failed to achieve RBC-TI at least 56 days prior to Week 48 were counted as non-responders.

End point type	Secondary

End point timeframe:

From Week 1 through Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percentage of Participants				
number (confidence interval 95%)	45.10 (37.05 to 53.34)	15.79 (8.43 to 25.96)		

Statistical analyses

Statistical analysis title	RBC-TI ≥ 8 weeks_4
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.526
upper limit	11.146

Statistical analysis title	RBC-TI ≥ 8 weeks_3
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Common Risk Difference on Response Rate
Point estimate	29.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	18.73
upper limit	40.36

Secondary: Change From Baseline in RBC Units Transfused Over Fixed 16-Week Period

End point title	Change From Baseline in RBC Units Transfused Over Fixed 16-Week Period

End point description:

Mean change in total number of Red Blood Cells (RBC) units transfused over a fixed 16-week period (Week 9-24 or Week 33-48) from the total number of RBC units transfused in the 16 weeks immediately on or prior to first dose of study treatment.

End point type	Secondary

End point timeframe:

At Baseline (16 weeks prior to first dose of study treatment) and Weeks 9 to 24 or Weeks 33 to 48

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	68		
Units: Units				
arithmetic mean (standard deviation)				
Weeks 9 to 24	-3.0 (± 5.17)	0.4 (± 4.25)		
Weeks 33 to 48	-4.9 (± 4.22)	-3.9 (± 7.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved a Modified Hematologic Erythroid Response (mHI-E) Over any Consecutive 56-Day Period

End point title	Percentage of Participants who Achieved a Modified Hematologic Erythroid Response (mHI-E) Over any Consecutive 56-Day Period

End point description:

A modified HI-E response was defined as the percentage of participants meeting the modified HI-E per the International Working Group (IWG) sustained over 56-day consecutive period during the Treatment period. For participants with a baseline RBC transfusion burden of ≥ 4 units/8 weeks, a mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks; for participants with baseline RBC transfusion burden of <4 units/8 weeks, mHI-E, was defined as a mean increase in hemoglobin of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions.

End point type	Secondary

End point timeframe:

Week 1 through 24 or Week 1 Through Week 48

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 1 Through Week 24	52.9 (44.72 to 61.05)	11.8 (5.56 to 21.29)		
Week 1 Through Week 48	58.8 (50.59 to 66.71)	17.1 (9.43 to 27.47)		

Statistical analyses

Statistical analysis title	mHI-E_2
Statistical analysis description: Week 1 - 48	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	mHI-E_1
Statistical analysis description: Week 1 -24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Participants Who Achieved a Mean Hemoglobin (Hgb) Increase of at Least 1.0 g/dL Over any Consecutive 56-Day Period in Absence of Red Blood Cells (RBC) Transfusions

End point title	Percentage of Participants Who Achieved a Mean Hemoglobin (Hgb) Increase of at Least 1.0 g/dL Over any Consecutive 56-Day Period in Absence of Red Blood Cells (RBC) Transfusions

End point description:

A mean hgb increase of ≥ 1.0 g/dL was analyzed as the percentage of participants with a hgb increase ≥ 1.0 g/dL compared with baseline (after applying the 14/3 day rule) that was sustained over any consecutive 56-day (8-week) period in the absence of RBC transfusions during the treatment period.

(Week 1 through Week 24 and Week 1 through Week 48).

End point type	Secondary

End point timeframe:

Week 1 though Week 24 and Week 1 through 48

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 1 Through Week 24	35.3 (27.75 to 43.42)	7.9 (2.95 to 16.40)		
Week 1 Through Week 48	41.2 (33.29 to 49.41)	10.5 (4.66 to 19.69)		

Statistical analyses

Statistical analysis title	Hgb increase_2

Statistical analysis description:

Week 1 Through Week 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Fisher exact

Statistical analysis title	Hgb increase_1

Statistical analysis description:

Week 1 Through Week 24

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Fisher exact

Secondary: Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 through Week 24

End point title	Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 through Week 24

End point description:

Duration of RBC-TI was defined as the longest duration of response for participants who achieved RBC-TI of ≥ 8 weeks during the treatment period Week 1 through Week 24. Participants who maintained RBC-TI through the end of the treatment period were censored at the date of IP discontinuation or death, whichever occurred first. Median was estimated from unstratified Kaplan Meier method.

End point type	Secondary

End point timeframe:

From start of study treatment to 16 weeks after last dose, up to approximately 70 weeks

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	10		
Units: Weeks				
median (confidence interval 95%)	30.6 (20.6 to 40.6)	13.6 (9.1 to 54.9)		

Statistical analyses

Statistical analysis title	RBC-TI Duration_1
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0445
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.446
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.196
upper limit	1.013

Secondary: Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 through Week 48

End point title	Duration of Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 through Week 48

End point description:

Duration of RBC-TI was defined as the longest duration of response for participants who achieved RBC-TI of ≥ 8 weeks during the treatment period Week 1 through Week 48. Participants who maintained RBC-TI through the end of the treatment period were censored at the date of IP discontinuation or death, whichever occurred first. Median was estimated from unstratified Kaplan Meier method.

End point type	Secondary

End point timeframe:

From start of study treatment to 16 weeks after last dose, up to approximately 76 weeks

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	12		
Units: Weeks				
median (confidence interval 95%)	30.6 (20.6 to 50.9)	18.6 (10.9 to 99999)		

Statistical analyses

Statistical analysis title	RBC-TI Duration_2
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5121
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.784
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.362
upper limit	1.699

Secondary: Mean Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Quality of Life Score

End point title	Mean Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Quality of Life Score

End point description:

The EORTC questionnaire is a validated health-related quality of life (HRQoL) measure applicable to participants with any cancer diagnosis. Version 3.0 of the questionnaire was used in the study.
It is composed of 30 items that address 15 domains, including one global health status, functional domains, and symptom domains. Domain scores are transformed to a 0 to 100 scale, where higher scores on the global quality of life score indicate better function. As such, a positive change from Baseline score indicates an improvement in quality of life.

End point type	Secondary

End point timeframe:

Baseline and Cycle 3, Day 1 (C3 D1), C5 D1, C7 D1, Week 25, every other cycle during extension phase (C1 D1, C3 D1, C5 D1, etc. up to C59 D1) and end of treatment. Each cycle is composed of 21 days.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (C3 D1)	-4.1 (± 21.01)	0.1 (± 15.95)		
C5 D1	-2.4 (± 20.73)	2.2 (± 17.13)		
C7 D1	-2.1 (± 23.04)	-0.6 (± 18.63)		
Week 25	-1.8 (± 21.75)	0.2 (± 18.88)		
Extension Phase C1 D1	0.0 (± 25.32)	6.3 (± 14.60)		
Extension Phase C3 D1	2.0 (± 19.68)	-3.9 (± 26.86)		
Extension Phase C5 D1	0.8 (± 18.40)	0.6 (± 20.04)		
Extension Phase C7 D1	-0.5 (± 20.03)	3.8 (± 20.87)		
Extension Phase C9 D1	-2.4 (± 18.42)	11.9 (± 19.75)		
Extension Phase C11 D1	-1.8 (± 19.53)	4.8 (± 24.47)		
Extension Phase C13 D1	-2.6 (± 20.84)	8.3 (± 24.15)		
Extension Phase C15 D1	3.1 (± 18.27)	4.2 (± 27.26)		
Extension Phase C17 D1	-0.6 (± 19.03)	13.9 (± 26.79)		
Extension Phase C19 D1	-1.6 (± 18.78)	-16.7 (± 14.43)		
Extension Phase C21 D1	3.1 (± 18.32)	4.2 (± 17.68)		
Extension Phase C23 D1	0.9 (± 17.84)	16.7 (± 99999)		
Extension Phase C25 D1	-2.0 (± 18.15)	16.7 (± 99999)		
Extension Phase C27 D1 0 subjects in Placebo.	2.5 (± 20.40)	99999 (± 99999)		
Extension Phase C29 D1 0 subjects in Placebo.	2.1 (± 21.12)	99999 (± 99999)		
Extension Phase C31 D1 0 subjects in Placebo.	-0.3 (± 15.93)	99999 (± 99999)		
Extension Phase C33 D1 0 subjects in Placebo.	-1.5 (± 19.41)	99999 (± 99999)		
Extension Phase C35 D1 0 subjects in Placebo.	3.6 (± 23.33)	99999 (± 99999)		
Extension Phase C37 D1 0 subjects in Placebo.	0.5 (± 22.04)	99999 (± 99999)		
Extension Phase C39 D1 0 subjects in Placebo.	0.3 (± 23.63)	99999 (± 99999)		
Extension Phase C41 D1 0 subjects in Placebo.	6.6 (± 20.11)	99999 (± 99999)		
Extension Phase C43 D1 0 subjects in Placebo.	4.8 (± 15.29)	99999 (± 99999)		
Extension Phase C45 D1 0 subjects in Placebo.	-2.2 (± 21.24)	99999 (± 99999)		
Extension Phase C47 D1 0 subjects in Placebo.	1.4 (± 19.08)	99999 (± 99999)		
Extension Phase C49 D1 0 subjects in Placebo.	-3.8 (± 16.40)	99999 (± 99999)		
Extension Phase C51 D1 0 subjects in Placebo.	8.3 (± 8.33)	99999 (± 99999)		
Extension Phase C53 D1 0 subjects in Placebo.	12.5 (± 10.76)	99999 (± 99999)		
Extension Phase C55 D1 0 subjects in Placebo.	2.8 (± 17.35)	99999 (± 99999)		
Extension Phase C57 D1 0 subjects in Placebo.	12.5 (± 5.89)	99999 (± 99999)		
Extension Phase C59 D1 0 subjects in Placebo.	16.7 (± 99999)	99999 (± 99999)		

End of Treatment	-9.2 (± 23.97)	-0.8 (± 23.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved a Hematologic Improvement in Neutrophil Response (HI-N) over any Consecutive 56-day Period

End point title	Percentage of Participants who Achieved a Hematologic Improvement in Neutrophil Response (HI-N) over any Consecutive 56-day Period

End point description:

Percentage of participants who achieved a hematologic improvement in neutrophil response (HI-N) per IWG criteria sustained over any consecutive 56-day (8-week) period, during the treatment period (Week 1 to Week 24 and Week 1 to Week 48) HI-N was defined as at least a 100% increase and an absolute increase > 0.5 X 10^9/L.

End point type	Secondary

End point timeframe:

Week 1 through Week 24 or Week 1 Through Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 1 Through Week 24	13.3 (1.66 to 40.46)	0 (0.00 to 30.85)		
Week 1 Through Week 48	20.0 (4.33 to 48.09)	10.0 (0.25 to 44.50)		

Statistical analyses

Statistical analysis title	HI-N_2

Statistical analysis description:

Week 1 - 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5127
Method	Cochran-Mantel-Haenszel

Statistical analysis title	HI-N_1
Statistical analysis description: Week 1 -24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2382
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Participants who Achieved a Hematologic Improvement in Platelet Response (HI-P) Over any Consecutive 56-day Period

End point title	Percentage of Participants who Achieved a Hematologic Improvement in Platelet Response (HI-P) Over any Consecutive 56-day Period

End point description:

Percentage of participants who achieved a hematologic improvement platelet response (HI-P) was defined as the percentage of participants meeting the HI-P criteria per the IWG sustained over any consecutive 56-day (8-week) period (Week 1 to Week 24 and Week 1 to Week 48) during the treatment period. HI – P reponse was defined as:
• Absolute increase of ≥ 30 X 10^9/L in platelets for participants starting with > 20 X 10^9/L platelets
• Increase in platelets from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%

End point type	Secondary

End point timeframe:

Week 1 through Week 24 or Week 1 Through Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 1 Through Week 24	50.0 (15.70 to 84.30)	33.3 (4.33 to 77.72)		
Week 1 Through Week 48	62.5 (24.49 to 91.48)	33.3 (4.33 to 77.72)		

Statistical analyses

Statistical analysis title	HI-P_2
Statistical analysis description: Week 1 - 48	
Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.298
Method	Cochran-Mantel-Haenszel

Statistical analysis title	HI-P_1
Statistical analysis description: Week 1 -24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5479
Method	Cochran-Mantel-Haenszel

Secondary: Change from Baseline in Mean Serum Ferritin

End point title	Change from Baseline in Mean Serum Ferritin
End point description: Mean change from baseline in mean serum ferritin was calculated as the difference of postbaseline mean serum ferritin (averaged over the specified timepoints) and baseline mean serum ferritin.	
End point type	Secondary
End point timeframe: Baseline and Week 9 through Week 24 and Week 33 through Week 48	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	74		
Units: ug/L				
least squares mean (standard error)				
Weeks 9-24	-2.7 (± 54.05)	226.5 (± 68.02)		
Weeks 33-48	-72.0 (± 74.76)	247.4 (± 140.96)		

Statistical analyses

Statistical analysis title	Ferritin_2
Statistical analysis description: Week 33 Through 48	
Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0294
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-319.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-606.3
upper limit	-32.7
Variability estimate	Standard error of the mean
Dispersion value	144.57

Statistical analysis title	Ferritin_1
Statistical analysis description:	
Week 9 Through 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0024
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-229.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-375.8
upper limit	-82.4
Variability estimate	Standard error of the mean
Dispersion value	74.43

Secondary: Change from Baseline in Mean Daily Dose of Iron Chelation Therapy (ICT)

End point title	Change from Baseline in Mean Daily Dose of Iron Chelation Therapy (ICT)

End point description:

Mean change from baseline in mean daily dose of ICT averaged over Week 9 to Week 24 or Week 33 to Week 48. For each participant, the mean change in daily dose of ICT was calculated as the difference of postbaseline mean daily dose and baseline mean daily dose.

End point type	Secondary

End point timeframe:

Baseline and Week 9 through Week 24 and Week 33 through Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	68		
Units: mg/day				
least squares mean (standard error)				
Weeks 9-24	10.0 (± 29.25)	51.0 (± 35.92)		
Weeks 33-48	-148.8 (± 46.13)	-123.8 (± 92.19)		

Statistical analyses

Statistical analysis title	ICT_1
Statistical analysis description: Weeks 9 Through 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3087
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-120.3
upper limit	38.2
Variability estimate	Standard error of the mean
Dispersion value	40.18

Statistical analysis title	ICT_2
Statistical analysis description: Weeks 33 Through 48	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7903
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-210.7
upper limit	160.8
Variability estimate	Standard error of the mean
Dispersion value	93.42

Secondary: Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 24

End point title	Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 24

End point description:

Time to RBC-TI was defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 24

End point type	Secondary

End point timeframe:

From first dose to Week 24 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	10		
Units: Days				
arithmetic mean (standard deviation)	17.2 (± 29.40)	26.0 (± 31.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 48

End point title	Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 48

End point description:

Time to RBC-TI was defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 48

End point type	Secondary

End point timeframe:

From first dose to Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	12		
Units: Days				
arithmetic mean (standard deviation)	40.3 (± 61.03)	57.2 (± 79.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Progressed to Acute Myeloid Leukemia (AML)

End point title	Percentage of Participants who Progressed to Acute Myeloid Leukemia (AML)

End point description:

Percentage of participants progressing to AML throughout the course of the study

End point type	Secondary

End point timeframe:

From randomization to study completion (up to approximately 57 months)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Percentage of Participants				
number (not applicable)	2.6	3.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Acute Myeloid Leukemia (AML) Progression

End point title	Time to Acute Myeloid Leukemia (AML) Progression

End point description:

Time to AML progression was defined as the time between randomization date and the first diagnosis of AML as per World Health Organization (WHO) classification of ≥ 20% blasts in peripheral blood or bone marrow. Participants with a diagnosis of AML were considered to have had an event, participants who did not progress to AML at the time of analysis were censored at the last assessment date which did not indicate progression to AML.
Median was not reached because of insufficient number of events

End point type	Secondary

End point timeframe:

From randomization to study completion (up to approximately 57 months)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[1]	3[2]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[1] - Median was not reached because of insufficient number of events

[2] - Median was not reached because of insufficient number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival was defined as the time from the date of study drug randomization to death due to any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for those who discontinued from the study or were lost to follow-up.

End point type	Secondary

End point timeframe:

From randomization to study completion (up to approximately 57 months)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76[3]		
Units: Months				
median (confidence interval 95%)	46.0 (42.0 to 99999)	99999 (43.1 to 99999)		

Notes:

[3] - Median not reached because of insufficient number of events

Statistical analyses

Statistical analysis title	OS
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.958
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.986

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	1.636

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point description:

The outcome measure describes the number of participants who experienced different types of Treatment-emergent adverse events (TEAEs).
TEAEs were defined as Adverse Events (AEs) that started on or after the day of the first dose and on or before 42 days after the last dose of IP.
The investigator determined the relationship of an AE to study drug based on the timing of the AE relative to drug administration and whether or not other drugs, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE was evaluated by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.0) where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death.

End point type	Secondary

End point timeframe:

From date of first dose up to 42 days after the last dose (up to approximately 66 weeks)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Participants				
≥ 1 TEAE	151	70		
≥ 1 Suspected Related TEAE	71	26		
≥ 1 Serious TEAE	66	23		
≥ 1 Suspected Related Serious TEAE	6	0		
≥ 1 TEAE CTCAE Toxicity Grade (GR) 5	8	4		
≥ 1 Suspected Related TEAE With CTCAE GR 5	0	0		
≥ 1 TEAE with CTCAE GR 3 or 4	86	34		
≥ 1 Suspected Related TEAE With CTCAE GR 3 or 4	13	3		
≥ 1 TEAE Leading to Dose Interruption	42	4		
≥ 1 TEAE Leading to Dose Reduction	9	0		
≥ 1 TEAE Leading to Study Drug Discontinuation	22	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Apparent Clearance (CL/F)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Apparent Clearance (CL/F)

End point description:

Apparent total plasma clearance was calculated as Dose/Area Under the Curve to infinity ().

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[4]		
Units: L/day				
geometric mean (geometric coefficient of variation)	0.516 (± 41.2)	()		

Notes:

[4] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Apparent Volume of Distribution of the Central Compartment (V1/F)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Apparent Volume of Distribution of the Central Compartment (V1/F)

End point description:

Apparent volume of distribution of luspatercept was calculated according to the equation Vz = (CL)/λ.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[5]		
Units: Liters				
geometric mean (geometric coefficient of variation)	9.68 (± 26.5)	()		

Notes:

[5] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Elimination Half-life (t1/2)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Elimination Half-life (t1/2)

End point description:

Terminal phase half-life was calculated according to the following equation: t1/2 = 0.693/λz.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[6]		
Units: Day				
geometric mean (geometric coefficient of variation)	13.0 (± 31.6)	()		

Notes:

[6] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Time to Reach Maximum Concentration (Tmax)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Time to Reach Maximum Concentration (Tmax)

End point description:

Tmax was defined as the observed time to maximum plasma concentration of luspatercept.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[7]		
Units: Day				
median (full range (min-max))	5.40 (3.12 to 6.69)	(to)		

Notes:

[7] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the First Dose (Cmax)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the First Dose (Cmax)

End point description:

Cmax was defined as the observed maximum plasma concentration, obtained directly from the observed concentration versus time.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[8]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	5.77 (± 20.5)	()		

Notes:

[8] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (Cmax) at Steady State

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (Cmax) at Steady State

End point description:

Cmax was defined as the observed maximum plasma concentration, obtained directly from the observed concentration at a steady state.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[9]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	9.17 (± 29.9)	()		

Notes:

[9] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Area Under the Curve at Steady State for Starting Dose (AUC^ss)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Area Under the Curve at Steady State for Starting Dose (AUC^ss)

End point description:

Area under the curve steady state was defined as the area under the plasma concentration-time curve for a steady state. calculated by the linear trapezoidal rule.

End point type	Secondary

End point timeframe:

Blood serum samples taken pre-dose at Cycle 1 Day 1 (C1, D1), C1 D8, C1 D15, C2 D1, C4 D1, C5 D8, C6 D1 and Week 25 visit, extension phase C4 D1 and Day 1 of every fourth treatment cycle thereafter.

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	0[10]		
Units: day/µg/mL				
geometric mean (geometric coefficient of variation)	145 (± 38.3)	()		

Notes:

[10] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Pre-Existing and/or Treatment-Emergent Antidrug Antibodies (ADA)

End point title	Participants with Pre-Existing and/or Treatment-Emergent Antidrug Antibodies (ADA)

End point description:

Number of participants with positive ADA prior to taking study drug and/or during study. A participant was counted as "treatment-emergent" if there was a positive post-baseline sample while the baseline sample was ADA negative, or there was a positive post-baseline sample with a titer ≥ 4-fold of the baseline titer while the baseline sample was ADA positive. A participant was counted as "preexisting" if the baseline sample was ADA positive and the participant was not qualified for "treatment-emergent."

End point type	Secondary

End point timeframe:

From randomization to 1 year post first dose

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	76		
Units: Participants				
Pre-Existing ADA	7	2		
Treatment Emergent ADA	11	3		
Treatment Emergent Neutralizing ADA	5	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from first dose to study completion (up to approximately 57 months). SAEs and Other AEs were assessed from first dose to 100 days following last dose (up to approximately 91 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo (Volume equivalent to experimental arm) SC on Day 1 of each 21-day treatment cycle

Reporting group title	Luspatercept

Reporting group description:

Luspatercept 1.0 mg/Kg SC on Day 1 of each 21-day treatment cycle

Serious adverse events	Placebo	Luspatercept	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 76 (30.26%)	66 / 153 (43.14%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			

subjects affected / exposed	1 / 76 (1.32%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blasts			
subjects affected / exposed	0 / 76 (0.00%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transformation to acute myeloid leukaemia			
subjects affected / exposed	1 / 76 (1.32%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mastocytosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Granulomatosis with polyangiitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 76 (2.63%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 76 (3.95%)	7 / 153 (4.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 76 (0.00%)	6 / 153 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 76 (3.95%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 76 (1.32%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal column injury			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic bone injury			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 76 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 76 (2.63%)	8 / 153 (5.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 76 (1.32%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Soft tissue infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			

subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 76 (1.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 76 (1.32%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 76 (1.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia moraxella			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Luspatercept	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 76 (82.89%)	145 / 153 (94.77%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 76 (7.89%)	16 / 153 (10.46%)	
occurrences (all)	8	53	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 76 (11.84%)	40 / 153 (26.14%)	
occurrences (all)	9	74	
Fatigue			
subjects affected / exposed	11 / 76 (14.47%)	46 / 153 (30.07%)	
occurrences (all)	14	70	
Influenza like illness			
subjects affected / exposed	3 / 76 (3.95%)	9 / 153 (5.88%)	
occurrences (all)	4	11	
Malaise			
subjects affected / exposed	3 / 76 (3.95%)	8 / 153 (5.23%)	
occurrences (all)	3	11	
Oedema peripheral			
subjects affected / exposed	13 / 76 (17.11%)	37 / 153 (24.18%)	
occurrences (all)	14	45	
Pyrexia			

subjects affected / exposed	6 / 76 (7.89%)	19 / 153 (12.42%)	
occurrences (all)	7	24	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 76 (0.00%)	8 / 153 (5.23%)	
occurrences (all)	0	8	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 76 (6.58%)	30 / 153 (19.61%)	
occurrences (all)	6	39	
Cough			
subjects affected / exposed	10 / 76 (13.16%)	35 / 153 (22.88%)	
occurrences (all)	13	50	
Epistaxis			
subjects affected / exposed	3 / 76 (3.95%)	12 / 153 (7.84%)	
occurrences (all)	3	13	
Oropharyngeal pain			
subjects affected / exposed	6 / 76 (7.89%)	6 / 153 (3.92%)	
occurrences (all)	6	6	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 76 (0.00%)	9 / 153 (5.88%)	
occurrences (all)	0	10	
Depression			
subjects affected / exposed	5 / 76 (6.58%)	9 / 153 (5.88%)	
occurrences (all)	5	10	
Insomnia			
subjects affected / exposed	4 / 76 (5.26%)	13 / 153 (8.50%)	
occurrences (all)	4	14	
Anxiety			
subjects affected / exposed	1 / 76 (1.32%)	9 / 153 (5.88%)	
occurrences (all)	1	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 76 (3.95%)	9 / 153 (5.88%)	
occurrences (all)	7	17	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 76 (1.32%)	10 / 153 (6.54%)	
occurrences (all)	3	22	
Weight decreased			
subjects affected / exposed	5 / 76 (6.58%)	9 / 153 (5.88%)	
occurrences (all)	5	16	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 76 (9.21%)	25 / 153 (16.34%)	
occurrences (all)	8	34	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 76 (6.58%)	11 / 153 (7.19%)	
occurrences (all)	5	12	
Tachycardia			
subjects affected / exposed	0 / 76 (0.00%)	8 / 153 (5.23%)	
occurrences (all)	0	9	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 76 (6.58%)	27 / 153 (17.65%)	
occurrences (all)	7	32	
Dizziness			
subjects affected / exposed	4 / 76 (5.26%)	35 / 153 (22.88%)	
occurrences (all)	4	52	
Syncope			
subjects affected / exposed	1 / 76 (1.32%)	10 / 153 (6.54%)	
occurrences (all)	1	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 76 (7.89%)	14 / 153 (9.15%)	
occurrences (all)	9	36	
Neutropenia			
subjects affected / exposed	7 / 76 (9.21%)	8 / 153 (5.23%)	
occurrences (all)	13	15	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 76 (0.00%)	12 / 153 (7.84%)	
occurrences (all)	0	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 76 (5.26%)	11 / 153 (7.19%)	
occurrences (all)	5	14	
Abdominal pain upper			
subjects affected / exposed	2 / 76 (2.63%)	11 / 153 (7.19%)	
occurrences (all)	2	12	
Constipation			
subjects affected / exposed	7 / 76 (9.21%)	21 / 153 (13.73%)	
occurrences (all)	11	28	
Diarrhoea			
subjects affected / exposed	8 / 76 (10.53%)	44 / 153 (28.76%)	
occurrences (all)	9	63	
Nausea			
subjects affected / exposed	6 / 76 (7.89%)	35 / 153 (22.88%)	
occurrences (all)	7	53	
Vomiting			
subjects affected / exposed	5 / 76 (6.58%)	14 / 153 (9.15%)	
occurrences (all)	5	21	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	4 / 76 (5.26%)	2 / 153 (1.31%)	
occurrences (all)	4	2	
Pruritus			
subjects affected / exposed	3 / 76 (3.95%)	11 / 153 (7.19%)	
occurrences (all)	3	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 76 (11.84%)	13 / 153 (8.50%)	
occurrences (all)	14	14	
Back pain			
subjects affected / exposed	6 / 76 (7.89%)	32 / 153 (20.92%)	
occurrences (all)	8	47	

Myalgia			
subjects affected / exposed	5 / 76 (6.58%)	13 / 153 (8.50%)	
occurrences (all)	6	14	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 76 (1.32%)	19 / 153 (12.42%)	
occurrences (all)	1	29	
Upper respiratory tract infection			
subjects affected / exposed	4 / 76 (5.26%)	19 / 153 (12.42%)	
occurrences (all)	5	27	
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	11 / 153 (7.19%)	
occurrences (all)	0	17	
Urinary tract infection			
subjects affected / exposed	4 / 76 (5.26%)	21 / 153 (13.73%)	
occurrences (all)	7	37	
Nasopharyngitis			
subjects affected / exposed	4 / 76 (5.26%)	18 / 153 (11.76%)	
occurrences (all)	5	26	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 76 (3.95%)	14 / 153 (9.15%)	
occurrences (all)	4	14	
Hyperglycaemia			
subjects affected / exposed	3 / 76 (3.95%)	12 / 153 (7.84%)	
occurrences (all)	3	14	
Hyperkalaemia			
subjects affected / exposed	1 / 76 (1.32%)	10 / 153 (6.54%)	
occurrences (all)	1	19	
Hyperuricaemia			
subjects affected / exposed	2 / 76 (2.63%)	12 / 153 (7.84%)	
occurrences (all)	2	22	
Iron overload			
subjects affected / exposed	3 / 76 (3.95%)	9 / 153 (5.88%)	
occurrences (all)	3	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2016	- Updates to criteria related to contraception measures - Added sites guidance for sample collection - Added language to exploratory markers - Updates to eligibility criteria - Updates to benefits/risk section
09 May 2017	- Updates to discontinuation criteria and dose modification - Clarification on sample collection modalities - Follow up period extension

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported