



## Clinical trial results:

### PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF LUSPATERCEPT (ACE-536) VERSUS PLACEBO IN ADULTS WHO REQUIRE REGULAR RED BLOOD CELL TRANSFUSIONS DUE TO BETA -THALASSEMIA The “BELIEVE” Trial

#### Summary

EudraCT number	2015-003224-31
Trial protocol	GB DE BG GR IT
Global end of trial date	05 January 2021

#### Results information

Result version number	v2 (current)
This version publication date	12 April 2023
First version publication date	11 January 2022
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	ACE-536-B-Thal-001
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##### 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	19 March 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 January 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the proportion of subjects treated with Luspatercept + BSC versus placebo + BSC who achieved erythroid response, defined as  $\geq 33\%$  reduction from baseline in transfusion burden (units RBCs/time) with a reduction of at least 2 units, from Week 13 to Week 24.

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	02 May 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	Malaysia: 39
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Thailand: 41
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Lebanon: 19
Country: Number of subjects enrolled	Tunisia: 17
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	336
EEA total number of subjects	100

Notes:

<b>Subjects enrolled per age group</b>	
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)	335
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

336 participants were randomized, 332 participants were 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	Subject, Investigator, Monitor, Carer

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Luspatercept + BSC
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Arm description:

Luspatercept (ACE-536) was administered subcutaneously (SC) at a starting dose level of 1 mg/kg once every 21 days. Participants could be dose-titrated to 1.25 mg/kg, but the maximum total dose should not exceed 120 mg, during the Treatment Period, the Long-term Treatment Period, and Open-Label Treatment Period. BSC = Best Supportive Care

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

Dosage and administration details:

1 mg/Kg SC Q3W

<b>Arm title</b>	Placebo + BSC
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Arm description:

Placebo (normal saline) was administered subcutaneously (SC) in volumes to match active treatment once every 21 days. BSC = Best Supportive Care

Arm type	Placebo
Investigational medicinal product name	0.9% Sodium Chloride
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Volume equal to investigational drug, SC Q3W

Number of subjects in period 1	Luspatercept + BSC	Placebo + BSC
Started	224	112
Participants Treated	223	109
Completed 24 weeks of treatment	211	102
Completed 48 weeks of treatment	202	96
Completed 96 weeks of treatment	155	3 <sup>[1]</sup>
Completed 144 weeks of treatment	125	0 <sup>[2]</sup>
Completed 192 weeks of treatment	6	0 <sup>[3]</sup>
Completed	6	6
Not completed	218	106
Adverse event, serious fatal	4	1
Consent withdrawn by subject	37	16
Physician decision	1	1
Transition to Rollover Protocol	169	82
Adverse event, non-fatal	4	-
Other reasons	3	5
Lack of efficacy	-	1

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones reflect the number of participants at a particular timepoint

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones reflect the number of participants at a particular timepoint

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones reflect the number of participants at a particular timepoint

## Baseline characteristics

### Reporting groups

Reporting group title	Luspatercept + BSC
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Reporting group description:

Luspatercept (ACE-536) was administered subcutaneously (SC) at a starting dose level of 1 mg/kg once every 21 days. Participants could be dose-titrated to 1.25 mg/kg, but the maximum total dose should not exceed 120 mg, during the Treatment Period, the Long-term Treatment Period, and Open-Label Treatment Period. BSC = Best Supportive Care

Reporting group title	Placebo + BSC
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Reporting group description:

Placebo (normal saline) was administered subcutaneously (SC) in volumes to match active treatment once every 21 days. BSC = Best Supportive Care

Reporting group values	Luspatercept + BSC	Placebo + BSC	Total
Number of subjects	224	112	336
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	223	112	335
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	32.2	31.9	-
standard deviation	± 10.67	± 9.89	-
Sex: Female, Male Units:			
Female	132	63	195
Male	92	49	141
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	2	7
Not Hispanic or Latino	218	107	325
Unknown or Not Reported	1	3	4
Race/Ethnicity, Customized Units: Subjects			
Asian	81	36	117
Black or African American	1	0	1
White	122	60	182
Not collected or reported	5	5	10
Other	15	11	26

## End points

### End points reporting groups

Reporting group title	Luspatercept + BSC
Reporting group description: Luspatercept (ACE-536) was administered subcutaneously (SC) at a starting dose level of 1 mg/kg once every 21 days. Participants could be dose-titrated to 1.25 mg/kg, but the maximum total dose should not exceed 120 mg, during the Treatment Period, the Long-term Treatment Period, and Open-Label Treatment Period. BSC = Best Supportive Care	
Reporting group title	Placebo + BSC
Reporting group description: Placebo (normal saline) was administered subcutaneously (SC) in volumes to match active treatment once every 21 days. BSC = Best Supportive Care	

### Primary: Percentage of Participants Who Achieved Erythroid Response - Week 13 to Week 24

End point title	Percentage of Participants Who Achieved Erythroid Response - Week 13 to Week 24
End point description: Erythroid Response was defined as red blood cell (RBC) transfusion burden reduction from baseline $\geq$ 33% with a reduction of at least 2 units during Week 13 - 24 compared to the 12-week interval on or prior to Dose 1 Day 1.	
End point type	Primary
End point timeframe: Baseline: Day -83 to Day 1; Treatment: Weeks 13 to Week 24	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Percentage of participants				
number (not applicable)	21.0	4.5		

### Statistical analyses

Statistical analysis title	Response - Week 13 to 24_1
Statistical analysis description: Odds ratio 95% confidence intervals (CIs), and p-value were estimated from the Cochran Mantel-Haenszel (CMH) test stratified by the geographical regions defined at randomization.	
Comparison groups	Luspatercept + BSC v Placebo + BSC

Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 <sup>[1]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.17
upper limit	14.53

Notes:

[1] - Significance level of 0.050 for 2-sided tests.

<b>Statistical analysis title</b>	Response - Week 13 to 24_3
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Common Risk Difference
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	23.1

<b>Statistical analysis title</b>	Response - Week 13 to 24_2
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Proportions
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	23.1

## Secondary: Percentage Of Participants Who Achieved $\geq$ 33% Reduction from Baseline in Transfusion Burden - Week 37 to Week 48

End point title	Percentage Of Participants Who Achieved $\geq$ 33% Reduction from Baseline in Transfusion Burden - Week 37 to Week 48
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End point description:

Percentage of participants who achieved a red blood cell (RBC) transfusion burden reduction from baseline  $\geq 33\%$  with a reduction of at least 2 units during Weeks 37 - 48 compared to the 12-week interval on or prior to Dose 1 Day 1.

End point type	Secondary
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End point timeframe:

Baseline: Day -83 to Day 1; Treatment: Weeks 37 to Week 48

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Percentage of participants				
number (not applicable)	19.6	3.6		

## Statistical analyses

Statistical analysis title	Response - Week 37 to 48
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Statistical analysis description:

Odds ratio 95% CIs, and p-value were estimated from the CMH test stratified by the geographical regions defined at randomization. To control the overall Type 1 error rate for outcomes 2-4, the testing procedure was implemented strictly in order: the test for this outcome was only conducted when there was evidence showing that erythroid response was achieved in the luspatercept group from Week 13 to Week 24 (primary endpoint).

Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.27
upper limit	18.26

Notes:

[2] - Significance level of 0.050 for 2-sided tests.

## Secondary: Percentage Of Participants Who Achieve $\geq 50\%$ Reduction from Baseline in Transfusion Burden - Week 37 to Week 48

End point title	Percentage Of Participants Who Achieve $\geq 50\%$ Reduction from Baseline in Transfusion Burden - Week 37 to Week 48
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End point description:

Percentage of participants who achieved a red blood cell (RBC) transfusion burden reduction from baseline  $\geq 50\%$  with a reduction of at least 2 units during Week 37 to Week 48 compared to the 12-week interval on or prior to Dose 1 Day 1.

End point type	Secondary
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End point timeframe:

Baseline: Day -83 to Day 1; Treatment: Week 37 to Week 48

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Percentage of participants				
number (not applicable)	10.3	0.9		

## Statistical analyses

Statistical analysis title	≥ 50% Reduction in transfusion burden_2
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Statistical analysis description:

Odds ratio, 95% CIs, and p-value were estimated from the Cochran-Mantel-Haenszel (CMH) test stratified by the geographical regions defined at randomization. To control the overall Type 1 error rate, the testing procedure was done strictly in order: the test for this outcome was only conducted when there was evidence showing erythroid response was achieved in the luspatercept group for the primary endpoint, and achievement of objective in the luspatercept group in outcomes 2+3.

Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0017 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	11.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	86.29

Notes:

[3] - Significance level of 0.050 for 2-sided tests.

## Secondary: Percentage Of Participants Who Achieve ≥ 50% Reduction from Baseline in Transfusion Burden - Week 13 to Week 24

End point title	Percentage Of Participants Who Achieve ≥ 50% Reduction from Baseline in Transfusion Burden - Week 13 to Week 24
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End point description:

Percentage of participants who achieved a red blood cell (RBC) transfusion burden reduction from baseline ≥ 50% with a reduction of at least 2 units during Weeks 13 - 24 compared to the 12-week interval on or prior to Dose 1 Day 1.

End point type	Secondary
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End point timeframe:

Baseline: Day -83 to Day 1; Treatment: Weeks 13 to Week 24

<b>End point values</b>	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Percentage of participants				
number (not applicable)	7.1	1.8		

## Statistical analyses

<b>Statistical analysis title</b>	≥ 50% Reduction in transfusion burden
Statistical analysis description:	
Odds ratio, 95% CIs, and p-value were estimated from the Cochran-Mantel-Haenszel (CMH) test stratified by the geographical regions defined at randomization. To control the overall Type 1 error rate, the testing procedure was done strictly in order: the test for this outcome was only conducted when there was evidence showing erythroid response was achieved in the luspatercept group for the primary endpoint, and 33% hematological improvement was achieved in the luspatercept group in outcome 2.	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0402 <sup>[4]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	18.79

Notes:

[4] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change from Baseline in Transfusion Burden - Week 13 to Week 24

End point title	Mean Change from Baseline in Transfusion Burden - Week 13 to Week 24
End point description:	
Baseline was defined as the total number of Red Blood Cells (RBC) units transfused during the 12-week interval on or prior to Dose 1 Day 1. This is compared to the total number of RBC units transfused during the 12-week interval from treatment weeks 13-24.	
End point type	Secondary
End point timeframe:	
Baseline: Day -83 to Day 1; Treatment: Weeks 13 to Week 24	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	102		
Units: RBC units				
arithmetic mean (standard deviation)	-0.67 ( $\pm$ 1.792)	0.66 ( $\pm$ 1.774)		

## Statistical analyses

Statistical analysis title	Transfusion burden
Statistical analysis description: LSM = least squares mean	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 <sup>[5]</sup>
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	-0.93

Notes:

[5] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change From Baseline In Liver Iron Concentration (LIC) At Week 48

End point title	Mean Change From Baseline In Liver Iron Concentration (LIC) At Week 48
End point description: Baseline was defined as the last value on or before the first dose of study drug was administered; if multiple values were present for the same date, the average of these values was used. If a participant had 1 postbaseline assessment, it was used as the Week 48 value. If a participant had multiple postbaseline assessments, the last one was used as the Week 48 value. The value of LIC was collected by magnetic resonance imaging. Participants with a LIC value > 43 mg/g were not included in the analysis.	
End point type	Secondary
End point timeframe: Baseline: Week -12 to Day -1; Treatment: Week 48	

<b>End point values</b>	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	99		
Units: mg/g dry weight				
arithmetic mean (standard deviation)	0.05 (± 5.770)	-0.00 (± 5.329)		

## Statistical analyses

<b>Statistical analysis title</b>	LIC - Change from baseline at Week 48
Statistical analysis description: Change from baseline at Week 48 P-value ANCOVA model with geographical regions defined at randomization and baseline LIC as covariates. LS = least square	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7598 <sup>[6]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1.51

Notes:

[6] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change From Baseline In Mean Daily Dose Of Iron Chelation Therapies (ICT) At Week 48

End point title	Mean Change From Baseline In Mean Daily Dose Of Iron Chelation Therapies (ICT) At Week 48
End point description: Three different types of Iron Chelation Therapy (ICT) were analyzed: 1. Deferasirox 2. Deferiprone 3. Deferoxamine Mesilate/Deferoxamine The baseline mean daily dose was calculated using the ICT dosage during the 12 weeks prior to first study drug administration and the postbaseline mean daily dose was calculated during the last 12 weeks of the 48-week double-blind Treatment Period or the last 12 weeks of the study treatment for early discontinued participants.	
End point type	Secondary
End point timeframe: Baseline: Day -83 to Day 1; Treatment: Week 37 to Week 48	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	66		
Units: mg				
arithmetic mean (standard deviation)				
Deferasirox	-105.0 (± 378.67)	-60.4 (± 297.11)		
Deferiprone	-229.1 (± 893.62)	-73.4 (± 614.80)		
Deferoxamine Mesilate/Deferoxamine	84.9 (± 523.45)	274.2 (± 613.05)		

## Statistical analyses

Statistical analysis title	ICT_1
Statistical analysis description:	
Change from baseline at Week 48 LS = least squares	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2552 [7]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-185.8
upper limit	49.7

Notes:

[7] - Significance level of 0.050 for 2-sided tests

Statistical analysis title	ICT_3
Statistical analysis description:	
Deferoxamine Mesilate / Deferoxamine: Change from baseline at Week 48 LS = least squares	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5186 [8]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-147.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-673.1
upper limit	378.5

Notes:

[8] - Significance level of 0.050 for 2-sided tests

<b>Statistical analysis title</b>	ICT_2
Statistical analysis description:	
Deferiprone: Change from baseline at Week 48 LS = least squares	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7746 <sup>[9]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-76.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-612.9
upper limit	460.1

Notes:

[9] - Significance level of 0.050 for 2-sided tests

## Secondary: Mean Change From Baseline In Mean Serum Ferritin At Week 48

End point title	Mean Change From Baseline In Mean Serum Ferritin At Week 48
End point description:	
For each participant, the baseline mean serum ferritin level was calculated during the 12 weeks prior to first study drug administration. The postbaseline mean serum ferritin level was calculated during the last 12 weeks of the 48-week double-blind Treatment Period or last 12 weeks of study treatment, if discontinued early. The change was calculated as the difference of post baseline mean serum ferritin level and baseline mean serum ferritin level.	
End point type	Secondary
End point timeframe:	
Baseline: Day -83 to Day 1; Treatment: Week 37 to Week 48	

<b>End point values</b>	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	101		
Units: µg/L				
arithmetic mean (standard deviation)	-247.19 (± 713.767)	100.38 (± 522.047)		

## Statistical analyses

<b>Statistical analysis title</b>	Ferritin - Change from baseline at Week 48
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Statistical analysis description:

Change from baseline at Week 48 LS = least squares

Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 <sup>[10]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-342.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-498.3
upper limit	-186.87

Notes:

[10] - Significance level of 0.050 for 2-sided tests

### Secondary: Mean Change From Baseline In Total Hip And Lumbar Spine Bone Mineral Density (BMD) At Week 48

End point title	Mean Change From Baseline In Total Hip And Lumbar Spine Bone Mineral Density (BMD) At Week 48
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End point description:

For BMD, the lumbar spine and total hip were measured at baseline and 48 weeks by dual energy x-ray absorptiometry (DXA). Baseline was defined as the last value on or before the first dose of study drug is administered; if multiple values are present for the same date, the average of these values was used. If during the 48 week double-blinded treatment period, a participant has only one assessment, it is counted as 'Week 48' visit; if a participant has multiple assessments, the last one is used as 'Week 48' visit. The analysis was done on the population that had at least 2 measurements.

End point type	Secondary
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End point timeframe:

Baseline: Day 1; Treatment: Week 48

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	95		
Units: gm/cm <sup>2</sup>				
arithmetic mean (standard deviation)				
Total Hip	0.01 (± 0.050)	0.01 (± 0.057)		
Lumbar Spine	-0.00 (± 0.063)	0.00 (± 0.078)		

### Statistical analyses

Statistical analysis title	Hip BMD - Change from baseline at Week 48
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Statistical analysis description:

LS = least squares



Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9201 <sup>[11]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.01

Notes:

[11] - Significance level of 0.050 for 2-sided tests.

<b>Statistical analysis title</b>	Spine BMD - Change from baseline at Week 48
Statistical analysis description:	
Lumbar Spine Bone Mineral Density: Change from baseline at Week 48 LS = least squares	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.462 <sup>[12]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01

Notes:

[12] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change From Baseline In Myocardial Iron At Week 48

End point title	Mean Change From Baseline In Myocardial Iron At Week 48
End point description:	
Myocardial Iron levels were measured by Magnetic Resonance Imaging (MRI), using MRI parameter T2* (Unit: ms). T2* values correlates with heart failure (HF) risk (e.g. T2*<6ms: high HF risk).	
End point type	Secondary
End point timeframe:	
Baseline: Day 1; Treatment: Week 48	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	102		
Units: ms				
arithmetic mean (standard deviation)	-1.83 ( $\pm$ 15.084)	-0.01 ( $\pm$ 6.780)		

## Statistical analyses

Statistical analysis title	Myocardial Iron - Change from baseline at Week 48
Statistical analysis description: Change from baseline at Week 48 LS = least square	
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0543 <sup>[13]</sup>
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.48
upper limit	0.04

Notes:

[13] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change From Baseline in the Transfusion-dependent Quality of Life (TranQol) Questionnaire At Week 24

End point title	Mean Change From Baseline in the Transfusion-dependent Quality of Life (TranQol) Questionnaire At Week 24
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End point description:

The TranQol is a self-administered quality of life tool developed for beta-thalassemia patients. The adult self-report version used in this study, includes 36 questions assessed on a 5-point response, that are grouped into 5 domains (Physical Health, Emotional Health, Sexual Health, Family Functioning, School/Career Functioning). Scores are calculated according to specific scoring algorithms developed by the authors. Both individual domains score and the total score range from 0 (worst) to 100 (best). Total Score and Physical Health domain score are reported. Positive change from baseline values indicate improvement.

End point type	Secondary
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End point timeframe:

Baseline: 4 weeks prior to Day 1; Treatment: Week 24

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	94		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Physical Health Domain Score	-1.5 ( $\pm$ 14.26)	-0.7 ( $\pm$ 14.24)		
Total Score	0.8 ( $\pm$ 11.56)	-0.4 ( $\pm$ 11.62)		

## Statistical analyses

Statistical analysis title	Physical Health Domain Score
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.666 <sup>[14]</sup>
Method	t-test, 2-sided

Notes:

[14] - Significance level of 0.050 for 2-sided tests.

Statistical analysis title	Total Score
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.384 <sup>[15]</sup>
Method	t-test, 2-sided

Notes:

[15] - Significance level of 0.050 for 2-sided tests.

## Secondary: Mean Change From Baseline in the 36-item Short Form Health Survey (SF-36) Questionnaire At Weeks 24

End point title	Mean Change From Baseline in the 36-item Short Form Health Survey (SF-36) Questionnaire At Weeks 24
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End point description:

The SF-36 (version 2) is a generic, self-administered instrument consisting of 8 multi-item scales that assess 8 health domains. The raw score for each health domain is transformed into a 0 (worst) to 100 (best) domain score. The 0–100 scale score for each health domain is further converted to normbased scores using a T-score transformation, with a mean of 50 and a standard deviation (SD) of 10. Higher norm-based T-scores indicate better health/QoL. The domains/summaries reported are: 1. Physical Functioning (Range of possible T-scores is 19.26 – 57.54) 2. General Health (Range of possible T-scores is 18.95 – 66.50) 3. Physical Component summary (PCS) (Range of possible T-scores is 5.02 – 79.78). Positive change from baseline values indicate improvement.

End point type	Secondary
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End point timeframe:

Baseline: 4 weeks prior to Day 1; Treatment: Weeks 24

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	103		
Units: T-score				
arithmetic mean (standard deviation)				
Physical Functioning Domain Score	-0.3 ( $\pm$ 6.93)	-0.2 ( $\pm$ 7.86)		
General Health Domain Score	0.4 ( $\pm$ 7.18)	0.3 ( $\pm$ 7.03)		
PCS	-0.4 ( $\pm$ 7.01)	-0.3 ( $\pm$ 7.97)		

## Statistical analyses

Statistical analysis title	Physical Functioning Domain
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.918 <sup>[16]</sup>
Method	t-test, 2-sided

Notes:

[16] - Significance level of 0.050 for 2-sided tests.

Statistical analysis title	General Health Domain
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.857 <sup>[17]</sup>
Method	t-test, 2-sided

Notes:

[17] - Significance level of 0.050 for 2-sided tests.

Statistical analysis title	PCS
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.839 <sup>[18]</sup>
Method	t-test, 2-sided

Notes:

[18] - Significance level of 0.050 for 2-sided tests.

## Secondary: Number of Days Spent in Higher Care Hospital Units

End point title	Number of Days Spent in Higher Care Hospital Units
End point description:	
Types of hospitals units considered to be 'higher care' are:	- Intensive Care Unit - Coronary Care Unit
End point type	Secondary

End point timeframe:

From informed consent signing (up to 12 weeks before start of treatment) to end of treatment (up to approximately 227 weeks)

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	5		
Units: Days				
arithmetic mean (standard deviation)	8.0 (± 23.70)	0.6 (± 0.55)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Who Utilized Healthcare Resources During Study

End point title	Number of Participants Who Utilized Healthcare Resources During Study
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End point description:

Number of participants who had any of the following types of Healthcare Resource Utilization (HRU): - a doctor office visit (non-study scheduled) - an emergency department visit - a hospitalization

End point type	Secondary
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End point timeframe:

From informed consent signing (up to 12 weeks before start of treatment) to end of treatment (up to approximately 227 weeks)

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Participants				
Doctor Office Visit	186	69		
Emergency Department Visit	71	22		
Hospital Admission	61	5		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Reduction in Transfusion Burden

End point title	Duration of Reduction in Transfusion Burden
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End point description:

Responders were defined as subjects who achieved ≥ 33% reduction or ≥ 50% reduction in Red Blood

Cells Transfusion (RBC-T) burden from baseline with a reduction of at least 2 RBC units during any rolling 12-week interval. The duration of reduction is calculated as Last Day of Response - First day of response +1

End point type	Secondary
End point timeframe:	
From first dose to end of study treatment (up to approximately 215 weeks)	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	39		
Units: Days				
arithmetic mean (standard deviation)				
Number of participants analyzed for 33%	627.3 (± 390.54)	224.0 (± 155.15)		
Number of participants analyzed for 50%	491.1 (± 386.37)	193.0 (± 142.51)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Of Participants Who Were Transfusion Independent For ≥ 8 Weeks During Treatment

End point title	Percentage Of Participants Who Were Transfusion Independent For ≥ 8 Weeks During Treatment
End point description:	
Transfusion independence was defined as the absence of any transfusion during any consecutive "rolling" 8-week time interval within the treatment period, i.e, Days 1 to 56, Days 2 to 57 and so on.	
End point type	Secondary
End point timeframe:	
From first dose through 3 weeks post last dose (up to approximately 218 weeks)	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	112		
Units: Percentage of participants				
number (not applicable)	12.1	1.8		

## Statistical analyses

Statistical analysis title	Transfusion independence >8 weeks
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**Statistical analysis description:**

Odds ratio 95% confidence intervals (CIs), and p-value were estimated from the Cochran Mantel-Haenszel (CMH) test stratified by the geographical regions defined at randomization.

Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0015 <sup>[19]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	32.9

Notes:

[19] - Significance level of 0.050 for 2-sided tests.

**Secondary: Longest Duration of Transfusion Independence**

End point title	Longest Duration of Transfusion Independence
End point description:	
Transfusion independence was defined as the absence of any transfusion during any consecutive "rolling" 8-week time interval within the treatment period, ie, Days 1 to 56, Days 2 to 57 and so on. Longest duration of transfusion independence was estimated based on Kaplan-Meier model.	
"99999"=N/A	
End point type	Secondary
End point timeframe:	
From first dose through 3 weeks post last dose (up to approximately 218 weeks)	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	2		
Units: Days				
median (confidence interval 95%)	72.0 (62.0 to 103.0)	71.5 (62.0 to 99999)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Erythroid Response**

End point title	Time to Erythroid Response
End point description:	
Time to erythroid response was defined as the time from first dose of the study drug to first erythroid response. This is reported for participants with a $\geq 33\%$ reduction from baseline in RBC transfusion	

burden (with a reduction of at least 2 units) for any 12-week interval., as well as participants with a  $\geq 50\%$  reduction from baseline in RBC transfusion burden (with a reduction of at least 2 units) for any 12-week interval.

End point type	Secondary
End point timeframe:	
From first dose to 48 weeks following first dose	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	39		
Units: Days				
arithmetic mean (standard deviation)				
$\geq 33\%$ Transfusion Burden Reduction	96.3 ( $\pm$ 163.92)	163.5 ( $\pm$ 148.78)		
$\geq 50\%$ Transfusion Burden Reduction	189.1 ( $\pm$ 257.69)	160.9 ( $\pm$ 160.17)		

## Statistical analyses

Statistical analysis title	$\geq 50\%$ Transfusion Burden Reduction
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7473 <sup>[20]</sup>
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	28.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-144.87
upper limit	201.34

Notes:

[20] - Significance level of 0.050 for 2-sided tests.

Statistical analysis title	$\geq 33\%$ Transfusion Burden Reduction
Comparison groups	Luspatercept + BSC v Placebo + BSC
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0195 <sup>[21]</sup>
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-67.27



Confidence interval	
level	95 %
sides	2-sided
lower limit	-123.63
upper limit	-10.91

Notes:

[21] - Significance level of 0.050 for 2-sided tests.

## Secondary: Post-Baseline Transfusion Event Frequency

End point title	Post-Baseline Transfusion Event Frequency
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End point description:

The number of transfusion events after start of study treatment were evaluated. For the definition of transfusion events, if multiple transfusions happen on the same date, they are counted as one event; if multiple transfusions happen on two consecutive dates, they are counted as one event; if multiple transfusions happen on three consecutive dates, they are counted as two events. Results are presented in 24-week intervals, up to 96 weeks after start of study treatment

End point type	Secondary
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End point timeframe:

From first dose through 3 weeks post last dose (up to approximately 218 weeks)

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	102		
Units: Number of transfusions				
arithmetic mean (standard deviation)				
Week 1 - 24	7.1 (± 2.03)	7.9 (± 1.65)		
Week 25 - 48	7.0 (± 2.02)	7.6 (± 1.61)		
Week 49 - 72	7.0 (± 2.04)	7.5 (± 1.28)		
Week 73 - 96	7.0 (± 2.13)	7.0 (± 1.00)		

## 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)
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[22]</sup>		
Units: L/day				
geometric mean (geometric coefficient of variation)	0.437 (± 38.5)	()		

Notes:

[22] - No study drug administered in this cohort

### 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)
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[23]</sup>		
Units: Liters				
geometric mean (geometric coefficient of variation)	7.08 (± 26.7)	()		

Notes:

[23] - No study drug administered in this cohort

### 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)
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[24]</sup>		
Units: days				
geometric mean (geometric coefficient of variation)	11.2 ( $\pm$ 25.7)	()		

Notes:

[24] - No study drug administered in this cohort

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (C<sub>max</sub>)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (C <sub>max</sub> )
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[25]</sup>		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	5.64 ( $\pm$ 25.1)	()		

Notes:

[25] - No study drug administered in this cohort

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration at Steady State for the Starting Dose (C<sub>max,ss</sub>)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration at Steady State for the Starting Dose (C <sub>max,ss</sub> )
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[26]</sup>		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	8.31 (± 30.1)	( )		

Notes:

[26] - No study drug administered in this cohort

### 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)
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End point description:

End point type	Secondary
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End point timeframe:

Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[27]</sup>		
Units: Days				
median (full range (min-max))	5.48 (3.35 to 7.74)	( to )		

Notes:

[27] - No study drug administered in this cohort

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Area Under the Concentration-Time Curve at Steady State for the Starting Dose (AUCss)

End point title	Pharmacokinetic (PK) Parameters: Bayesian Estimate of Area Under the Concentration-Time Curve at Steady State for the Starting Dose (AUCss)
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End point description:

End point type	Secondary
End point timeframe:	
Blood serum samples taken pre-dose and on Days 1, 22, 64, 85, 106, 127, 169, 211, 253, 295, 337	

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	0 <sup>[28]</sup>		
Units: day*µg/mL				
geometric mean (geometric coefficient of variation)	129 (± 36.0)	( )		

Notes:

[28] - No study drug administered in this cohort

## Statistical analyses

No statistical analyses for this end point

## Secondary: Participants with Treatment-Emergent Adverse Events (TEAE)

End point title	Participants with Treatment-Emergent Adverse Events (TEAE)
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End point description:

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen during the course of a study. A serious AE is any AE occurring at any dose that - Results in death - Is life-threatening - Requires or prolongs existing inpatient hospitalization - Results in persistent or significant disability/incapacity - Is a congenital anomaly/birth defect - Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03): - Grade 1 = Mild - Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention) - Grade 3 = Severe (limitation in activity; medical intervention required) - Grade 4 = Life-threatening - Grade 5 = Death

End point type	Secondary
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End point timeframe:

From first dose to 90 days following last dose (up to approximately 52 months)

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	109		
Units: Participants				
≥ 1 Treatment-emergent adverse event (TEAE)	219	102		
Serious TEAE	53	8		
Grade ≥ 3 TEAE	84	19		
Treatment-related TEAE	135	31		
Treatment-related Serious TEAE	13	0		
Treatment-related TEAE ≥ Grade 3	27	1		
TEAE leading to death	2	1		
Trt-related TEAE leading to death	0	0		
TEAE leading to dose reduction	10	3		

TEAE leading to dose delay	46	11		
TEAE leading to drug discontinuation	25	2		
Trt-related TEAE leading to dose reduction	9	2		
Trt-related TEAE leading to dose delay	15	3		
Trt-related TEAE leading to drug discontinuation	20	1		

## 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)
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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  $\geq$  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
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End point timeframe:

Timeframe: pre-dose, Day 1, Days 22, 64, 106, 148, 232, 316

End point values	Luspatercept + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	109		
Units: Participants				
Pre-existing	2	1		
Treatment-emergent	4	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 (approximately 56 months) SAEs and NSAEs were assessed from first dose to 90 days following last dose (up to approximately 52 months)

Adverse event reporting additional description:

Adverse events were collected in all participants who received at least 1 dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo (normal saline) was administered subcutaneously (SC) in volumes to match active treatment once every 21 days. BSC = Best Supportive Care

Reporting group title	Luspatercept
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Reporting group description:

Luspatercept (ACE-536) was administered subcutaneously (SC) at a starting dose level of 1 mg/kg once every 21 days. Participants could be dose-titrated to 1.25 mg/kg, but the maximum total dose should not exceed 120 mg, during the Treatment Period, the Long-term Treatment Period, and Open-Label Treatment Period. BSC = Best Supportive Care

Serious adverse events	Placebo	Luspatercept	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 109 (7.34%)	53 / 223 (23.77%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute erythroid leukaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 109 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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			
Pyrexia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			



subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Coombs direct test positive			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood uric acid increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thermal burn			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac iron overload			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 109 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombotic stroke			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuritis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Pancytopenia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extramedullary haemopoiesis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 109 (0.00%)	4 / 223 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 109 (1.83%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			

subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Epstein-Barr virus infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 109 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder empyema			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 109 (0.92%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			

subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 223 (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 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic abscess			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			



subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 109 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 223 (0.45%)	
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 / 109 (0.00%)	1 / 223 (0.45%)	
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 %

<b>Non-serious adverse events</b>	Placebo	Luspatercept	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 109 (87.16%)	211 / 223 (94.62%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 109 (3.67%)	12 / 223 (5.38%)	
occurrences (all)	11	28	
Liver iron concentration increased			
subjects affected / exposed	2 / 109 (1.83%)	12 / 223 (5.38%)	
occurrences (all)	2	13	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 109 (7.34%)	8 / 223 (3.59%)	
occurrences (all)	8	8	
Transfusion reaction			
subjects affected / exposed	5 / 109 (4.59%)	12 / 223 (5.38%)	
occurrences (all)	6	14	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 109 (2.75%)	23 / 223 (10.31%)	
occurrences (all)	3	43	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 109 (4.59%)	29 / 223 (13.00%)	
occurrences (all)	6	56	
Lethargy			
subjects affected / exposed	4 / 109 (3.67%)	12 / 223 (5.38%)	
occurrences (all)	11	27	
Headache			
subjects affected / exposed	27 / 109 (24.77%)	78 / 223 (34.98%)	
occurrences (all)	69	265	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	11 / 109 (10.09%)	26 / 223 (11.66%)	
occurrences (all)	35	55	
Fatigue			
subjects affected / exposed	16 / 109 (14.68%)	38 / 223 (17.04%)	
occurrences (all)	21	96	
Influenza like illness			
subjects affected / exposed	8 / 109 (7.34%)	21 / 223 (9.42%)	
occurrences (all)	12	31	
Injection site pain			
subjects affected / exposed	3 / 109 (2.75%)	12 / 223 (5.38%)	
occurrences (all)	3	22	
Pyrexia			
subjects affected / exposed	24 / 109 (22.02%)	47 / 223 (21.08%)	
occurrences (all)	37	68	
Pain			
subjects affected / exposed	4 / 109 (3.67%)	14 / 223 (6.28%)	
occurrences (all)	4	17	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 109 (3.67%)	12 / 223 (5.38%)	
occurrences (all)	6	14	
Abdominal pain			
subjects affected / exposed	7 / 109 (6.42%)	30 / 223 (13.45%)	
occurrences (all)	11	42	
Abdominal pain upper			
subjects affected / exposed	8 / 109 (7.34%)	25 / 223 (11.21%)	
occurrences (all)	14	36	
Diarrhoea			
subjects affected / exposed	14 / 109 (12.84%)	41 / 223 (18.39%)	
occurrences (all)	17	61	
Vomiting			
subjects affected / exposed	8 / 109 (7.34%)	30 / 223 (13.45%)	
occurrences (all)	15	44	
Dyspepsia			
subjects affected / exposed	1 / 109 (0.92%)	19 / 223 (8.52%)	
occurrences (all)	2	21	

Nausea subjects affected / exposed occurrences (all)	6 / 109 (5.50%) 8	29 / 223 (13.00%) 43	
Toothache subjects affected / exposed occurrences (all)	5 / 109 (4.59%) 7	15 / 223 (6.73%) 17	
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all)	6 / 109 (5.50%) 7	12 / 223 (5.38%) 21	
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 109 (2.75%) 4  13 / 109 (11.93%) 17  13 / 109 (11.93%) 13	21 / 223 (9.42%) 32  48 / 223 (21.52%) 82  41 / 223 (18.39%) 54	
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	4 / 109 (3.67%) 5	17 / 223 (7.62%) 36	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Back pain subjects affected / exposed occurrences (all)  Musculoskeletal chest pain subjects affected / exposed occurrences (all)  Musculoskeletal pain	15 / 109 (13.76%) 26  33 / 109 (30.28%) 60  8 / 109 (7.34%) 11	51 / 223 (22.87%) 113  72 / 223 (32.29%) 196  8 / 223 (3.59%) 8	

subjects affected / exposed	11 / 109 (10.09%)	21 / 223 (9.42%)	
occurrences (all)	13	24	
Bone pain			
subjects affected / exposed	9 / 109 (8.26%)	50 / 223 (22.42%)	
occurrences (all)	14	124	
Neck pain			
subjects affected / exposed	9 / 109 (8.26%)	14 / 223 (6.28%)	
occurrences (all)	12	28	
Myalgia			
subjects affected / exposed	11 / 109 (10.09%)	28 / 223 (12.56%)	
occurrences (all)	17	35	
Osteoporosis			
subjects affected / exposed	7 / 109 (6.42%)	13 / 223 (5.83%)	
occurrences (all)	7	13	
Pain in extremity			
subjects affected / exposed	12 / 109 (11.01%)	33 / 223 (14.80%)	
occurrences (all)	13	89	
Spinal pain			
subjects affected / exposed	5 / 109 (4.59%)	12 / 223 (5.38%)	
occurrences (all)	7	15	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	9 / 109 (8.26%)	18 / 223 (8.07%)	
occurrences (all)	11	22	
Nasopharyngitis			
subjects affected / exposed	4 / 109 (3.67%)	17 / 223 (7.62%)	
occurrences (all)	4	21	
Influenza			
subjects affected / exposed	8 / 109 (7.34%)	25 / 223 (11.21%)	
occurrences (all)	12	36	
Pharyngitis			
subjects affected / exposed	15 / 109 (13.76%)	36 / 223 (16.14%)	
occurrences (all)	16	57	
Tonsillitis			
subjects affected / exposed	2 / 109 (1.83%)	16 / 223 (7.17%)	
occurrences (all)	2	24	

Urinary tract infection subjects affected / exposed occurrences (all)	6 / 109 (5.50%) 7	13 / 223 (5.83%) 15	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	43 / 109 (39.45%) 65	93 / 223 (41.70%) 212	
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	0 / 109 (0.00%) 0	16 / 223 (7.17%) 23	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2015	-Exploratory endpoints changes -Study design changes -Eligibility criteria changes
21 April 2017	-Dose modification changes

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported