Clinical trial results:
A Phase 2, Double-Blind, Randomized, Placebo-Controlled Multicenter Study to Determine the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo in Adults With Non-Transfusion Dependent Beta ()-Thalassemia (The BEYOND™ Study)

Summary

EudraCT number	2015-003225-33
Trial protocol	GB GR IT
Global end of trial date	28 November 2022

Results information

Result version number	v1 (current)
This version publication date	14 December 2023
First version publication date	14 December 2023

Trial information

Trial identification

Sponsor protocol code	ACE-536-B-THAL-002

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	Chaussee 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	14 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of luspatercept versus placebo on anemia, as measured by mean Hb values in the absence of transfusions over continuous 12-week intervals, from Week 13 to Week 24, compared to baseline

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	01 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 38
Country: Number of subjects enrolled	Lebanon: 17
Country: Number of subjects enrolled	Greece: 36
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	145
EEA total number of subjects	79

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	140
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

145 subjects were treated

Period 1

Period 1 title	Blinded Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Luspatercept

Arm description:

Luspatercept was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle). The starting dose level was 1.00 mg/kg and could be escalated to 1.25 mg/kg and/or reduced to 0.80, 0.60, and 0.45 mg/kg. Participants were treated for a minimum of 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection once every 3 weeks for at least 48 weeks. Starting dose 1.00 mg/kg

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.

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

Dosage and administration details:

Subcutaneous injection of 0.9% sodium chloride once every 3 weeks for at least 48 weeks.

Number of subjects in period 1	Luspatercept	Placebo
Started	96	49
Completed	68	18
Not completed	28	31
Adverse event, serious fatal	1	-
Consent withdrawn by subject	17	10
Physician decision	1	-
Adverse event, non-fatal	5	4
Noncompliance with study drug	1	-
Other reasons	1	-
Lack of efficacy	2	17

Period 2

Period 2 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.

Arm type	Experimental
Investigational medicinal product name	Luspatercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection once every 3 weeks for at least 48 weeks. Starting dose 1.00 mg/kg

Number of subjects in period 2[1]	Placebo
Started	38
Completed	27
Not completed	11
Consent withdrawn by subject	6

Adverse event, non-fatal	3
Other reasons	1
Lost to follow-up	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All participants in the Luspatercept arm completed treatment but participants in the placebo arm were eligible to receive Luspatercept treatment

Baseline characteristics

Reporting groups	
Reporting group title	Luspatercept
Reporting group description:	
Luspatercept was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle). The starting dose level was 1.00 mg/kg and could be escalated to 1.25 mg/kg and/or reduced to 0.80, 0.60, and 0.45 mg/kg. Participants were treated for a minimum of 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.	

Reporting group values	Luspatercept	Placebo	Total
Number of subjects	96	49	145
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
85 years and over	0	0	0
Adults (18-64 years)	93	47	140
From 65-84 years	3	2	5
Age Continuous Units: Years			
arithmetic mean	39.3	41.1	
standard deviation	± 13.24	± 11.90	-
Sex: Female, Male Units: Participants			
Female	56	26	82
Male	40	23	63
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	94	48	142
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	31	13	44
White	59	28	87
Other	6	8	14

End points

End points reporting groups

Reporting group title	Luspatercept
Reporting group description:	
Luspatercept was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle). The starting dose level was 1.00 mg/kg and could be escalated to 1.25 mg/kg and/or reduced to 0.80, 0.60, and 0.45 mg/kg. Participants were treated for a minimum of 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.	
Reporting group title	Placebo
Reporting group description:	
Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.	

Primary: Percentage of Participants Achieving Erythroid Response (Week 13 to Week 24)

End point title	Percentage of Participants Achieving Erythroid Response (Week 13 to Week 24)
End point description:	
Erythroid Response is defined as an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Weeks 13 to 24 of treatment in the absence of transfusions. Baseline hemoglobin (Hb) is the average of 2 or more Hb measurements at least 1 week apart within 4 weeks prior to Dose 1.	
End point type	Primary
End point timeframe:	
From Week 13 to Week 24 of study treatment	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percent of Participants				
number (confidence interval 95%)	77.1 (67.4 to 85.0)	0.0 (0.0 to 7.3)		

Statistical analyses

Statistical analysis title	Erythroid Response
Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Erythroid Response
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	77.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	68.7
upper limit	85.5

Statistical analysis title	Erythroid Response
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in proportions
Point estimate	77.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.4
upper limit	87

Secondary: Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score (Week 13 to Week 24)

End point title	Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score (Week 13 to Week 24)

End point description:

The NTDT-PRO assesses the severity of anemia-related symptoms with a daily recall of symptoms composed of 6 items: 1. Tiredness (lack of energy) when not doing physical activity 2. Tiredness when doing physical activity 3. Weakness (lack of strength) when not doing physical activity 4. Weakness when doing physical activity 5. Shortness of breath when not doing physical activity 6. Shortness of breath when doing physical activity. The Tiredness/Weakness (T/W) domain score is the average score of items 1 through 4 above. T/W domain score ranges from 0 (best outcome, no tiredness/weakness) to 10 (worst outcome, extreme tiredness/weakness). Weekly T/W Scores are the average of daily scores for that week. The mean of weekly scores over a continuous 12-week period (from Week 13 to Week

24) are compared to the T/W Domain Score at baseline. Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 13.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 13 through week 24)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	48		
Units: Score on a scale				
least squares mean (standard error)	-0.68 (± 0.176)	-0.20 (± 0.240)		

Statistical analyses

Statistical analysis title	NTDT-PRO T/W
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0924
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.08

Secondary: Mean Change From Baseline in Hemoglobin Values in the Absence of Transfusion (Week 13 to Week 24)

End point title	Mean Change From Baseline in Hemoglobin Values in the Absence of Transfusion (Week 13 to Week 24)

End point description:

Mean change from baseline in mean of hemoglobin (Hb) values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions. Baseline was defined as the average of 2 or more Hb measurements at least 1 week apart within 4 weeks before Dose 1 Day 1.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 13 through week 24)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	47		
Units: g/dL				
least squares mean (standard error)	1.48 (± 0.078)	0.07 (± 0.108)		

Statistical analyses

Statistical analysis title	Hemoglobin
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.67

Secondary: Percentage of Participants Achieving Erythroid Response (Week 37 to Week 48)

End point title	Percentage of Participants Achieving Erythroid Response (Week 37 to Week 48)

End point description:

Erythroid Response is defined as an increase from baseline ≥1.0 g/dL in mean of hemoglobin values over a continuous 12-week interval from Weeks 37 to 48 of treatment in the absence of transfusions. Baseline hemoglobin (Hb) is the average of 2 or more Hb measurements at least 1 week apart within 4 weeks prior to Dose 1.

End point type	Secondary

End point timeframe:

Assessed over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percentage of Participants				
number (confidence interval 95%)	70.8 (60.7 to 79.7)	2.0 (0.1 to 10.9)		

Statistical analyses

Statistical analysis title	Erythroid Response
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	68.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.3
upper limit	80.4

Secondary: Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Shortness of Breath (SoB) Domain Score (Week 13 to Week 24)

End point title	Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Shortness of Breath (SoB) Domain Score (Week 13 to Week 24)

End point description:

The NTDT-PRO V2.1 assess the severity of anemia-related symptoms associated with NTD β-thalassemia. It is a daily electronic diary with recall of symptoms during the past 24 hours, composed of 6 items: 1. Tiredness (lack of energy) when not doing physical activity 2. Tiredness (lack of energy) when doing physical activity 3. Weakness (lack of strength) when not doing physical activity 4. Weakness (lack of strength) when doing physical activity 5. Shortness of breath when not doing physical activity 6. Shortness of breath when doing physical activity. The Shortness of Breath (SoB) domain score represents the average score of items 5 and 6 above. SoB domain score ranges from 0 (best outcome, no shortness of breath) to 10 (worst outcome, extreme shortness of breath). Weekly SoB Scores represent the average of daily scores for that week. The mean of weekly scores over a continuous 12 week period (from Week 13 to Week 24) are compared to the SoB Domain Score at baseline.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 13 through week 24)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	48		
Units: Score on a scale				
least squares mean (standard error)	-0.46 (± 0.168)	0.02 (± 0.228)		

Statistical analyses

Statistical analysis title	NTD-PRO
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0721
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	0.04

Secondary: Mean Change from Baseline in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 13 to Week 24)

End point title	Mean Change from Baseline in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 13 to Week 24)

End point description:

The FACIT-F is a multidimensional, self-report quality of life instrument which includes the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire (27 items over 4 different domains), and the Fatigue subscale (FS) component (13 items). FACIT-F version 4 has been used for this study. For the Fatigue subscale, each of the 13 items is scored from 0 (“not at all”) to 4 (“very much”). The scores from individual items are summed to generated the final FS score, which ranges from 0 (best outcome) to 52 (worst outcome). The questionnaire is completed every other dose, and the mean of FS scores from Week 13 to Week 24 is compared to the FS score at baseline (last score available before start of study treatment). Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 13.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 13 through week 24)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	43		
Units: Score on a scale				
least squares mean (standard error)	1.64 (± 0.774)	0.26 (± 1.066)		

Statistical analyses

Statistical analysis title	FACT-IF
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2641
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	3.83

Secondary: Mean Change from Baseline in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 37 to Week 48)

End point title	Mean Change from Baseline in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 37 to Week 48)

End point description:

The FACIT-F is a multidimensional, self-report quality of life instrument which includes the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire (27 items over 4 different domains), and the Fatigue subscale (FS) component (13 items). FACIT-F version 4 has been used for this study. For the Fatigue subscale, each of the 13 items is scored from 0 (“not at all”) to 4 (“very much”). The scores from individual items are summed to generated the final FS score, which ranges from 0 (best outcome) to 52 (worst outcome). The questionnaire is completed every other dose, and the mean of FS scores from Week 37 to Week 48 is compared to the FS score at baseline (last score available before start of study treatment). Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 37.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	33		
Units: Score on a scale				
least squares mean (standard error)	2.43 (± 0.763)	0.24 (± 1.150)		

Statistical analyses

Statistical analysis title	FACT-IF
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0959
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	4.78

Secondary: Mean Change From Baseline in Hemoglobin Values in the Absence of Transfusion (Week 37 to Week 48)

End point title	Mean Change From Baseline in Hemoglobin Values in the Absence of Transfusion (Week 37 to Week 48)

End point description:

Mean change from baseline in mean of hemoglobin (Hb) values over a continuous 12-week interval from Week 37 to Week 48 in the absence of transfusions. Baseline was defined as the average of 2 or more Hb measurements at least 1 week apart within 4 weeks before Dose 1 Day 1.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	34		
Units: g/dL				
least squares mean (standard error)	1.50 (± 0.083)	0.01 (± 0.130)		

Statistical analyses

Statistical analysis title	Hemoglobin values
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.79

Secondary: Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Shortness of Breath (SoB) Domain Score (Week 37 to Week 48)

End point title	Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Shortness of Breath (SoB) Domain Score (Week 37 to Week 48)

End point description:

NTDT-PRO V2.1 assess the severity of anemia-related symptoms. It is a daily recall of symptoms during the past 24 hours, composed of 6 items: 1. Tiredness (lack of energy) when not doing physical activity 2. Tiredness when doing physical activity 3. Weakness (lack of strength) when not doing physical activity 4. Weakness when doing physical activity 5. Shortness of breath when not doing physical activity 6. Shortness of breath when doing physical activity. The Shortness of Breath (SoB) domain score represents the average score of items 5 and 6 above. SoB domain score ranges from 0 (best outcome, no shortness of breath) to 10 (worst outcome, extreme shortness of breath). Weekly SoB Scores represent the average of daily scores for that week. The mean of weekly scores over a continuous 12-week period (from Week 37 to Week 48) are compared to the SoB Domain Score at baseline. Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 37.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	28		
Units: Score on a scale				
least squares mean (standard error)	-0.59 (± 0.212)	0.47 (± 0.320)		

Statistical analyses

Statistical analysis title	NTD-PRO SOB
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0047
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.33

Secondary: Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score (Week 37 to Week 48)

End point title	Mean Change From Baseline in Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score (Week 37 to Week 48)

End point description:

NTDT-PRO V2.1 assess the severity of anemia-related symptoms. It's a daily recall of symptoms during the past 24 hours, composed of 6 items: 1. Tiredness (lack of energy) when not doing physical activity 2. Tiredness when doing physical activity 3. Weakness (lack of strength) when not doing physical activity 4. Weakness when doing physical activity 5. Shortness of breath when not doing physical activity 6. Shortness of breath when doing physical activity. The Tiredness/Weakness (T/W) domain score represents the average score of items 1 through 4 above. T/W domain score ranges from 0 (best outcome, no tiredness/weakness) to 10 (worst outcome, extreme tiredness/weakness). Weekly T/W Scores represent the average of daily scores for that week. The mean of weekly scores over a continuous 12-week period (from Week 37 to Week 48) are compared to the T/W Domain Score at baseline. Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 37.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	28		
Units: Score on a scale				
least squares mean (standard error)	-0.78 (± 0.229)	0.01 (± 0.347)		

Statistical analyses

Statistical analysis title	NTD-PRO
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.051
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	0

Secondary: Percentage of Participants with an Increase from Baseline ≥ 3 in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 13 to Week 24)

End point title	Percentage of Participants with an Increase from Baseline ≥ 3 in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 13 to Week 24)

End point description:

The FACIT-Fatigue, is a multidimensional, self-report quality of life instrument. It consists of 27 core items, the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire, which assesses patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by a 13-item measure designed to capture cancer-related fatigue, the Fatigue subscale (FS). The items are measured on a response scale with five options (0 = not at all to 4 = very much). Participants completed the questionnaire at screening and every other dose. Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 13. Score is calculated by multiplying the sum of item scores by the n of items in the scale, then divided by n of items answered.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 13 through week 24)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	47		
Units: Percent of Participants				
number (confidence interval 95%)	40.4 (30.4 to 51.0)	27.7 (15.6 to 42.6)		

Statistical analyses

Statistical analysis title	FACT-IF
Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1359
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	4

Secondary: Mean Change From Baseline in the Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores of the Medical Outcomes Study 36-Item Short Form (SF-36)

End point title	Mean Change From Baseline in the Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores of the Medical Outcomes Study 36-Item Short Form (SF-36)

End point description:

The SF-36v2 is a 36-item generic PRO questionnaire used to assess patient-reported outcomes. The SF-36 yields scores for 8 domains of health: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH) as well as physical component summary (PCS) and mental component summary (MCS) scores. Scores from each of the 8 domains of health are first normalized based on US general population means, then aggregated and transformed so that the scores from each of the 8 domains of health will contribute differently to the determination of PCS and MCS summary scores. PCS and MCS scores range from 0 to 100, with higher scores indicating a better quality of life. Baseline is defined as the last value taken on or before the first dose of study drug administered.

End point type	Secondary

End point timeframe:

From baseline to Week 24 and from baseline to Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	37		
Units: Score on a scale				
least squares mean (standard error)				
Physical Component Summary (PCS) up to Week 24	1.00 (± 0.499)	-0.38 (± 0.684)		
Physical Component Summary (PCS) up to Week 48	1.23 (± 0.571)	-0.52 (± 0.822)		
Mental Component Summary (MCS) up to Week 24	0.83 (± 0.674)	-0.71 (± 0.947)		
Mental Component Summary (MCS) up to Week 48	0.81 (± 0.784)	-1.89 (± 1.152)		

Statistical analyses

Statistical analysis title	PCS
Statistical analysis description:	
Mean change from baseline in SF-36 PCS to Week 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0847
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	2.96

Statistical analysis title	PCS
Statistical analysis description:	
Mean change from baseline in SF-36 PCS to Week 48	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0712
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	3.65

Statistical analysis title	MCS
Statistical analysis description:	
Mean change from baseline in SF-36 MCS to Week 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1633
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	3.72

Statistical analysis title	MCS

Statistical analysis description:

Mean change from baseline in SF-36 MCS to Week 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0469
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	5.36

Secondary: Percentage of Participants with an Increase from Baseline ≥ 3 in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 37 to Week 48)

End point title	Percentage of Participants with an Increase from Baseline ≥ 3 in Mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Fatigue Subscale Score (Week 37 to Week 48)

End point description:

The FACIT-Fatigue, is a multidimensional, self-report quality of life instrument. It consists of 27 core items, the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire, which assesses patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by a 13-item measure designed to capture cancer-related fatigue, the Fatigue subscale (FS). The items are measured on a response scale with five options (0 = not at all to 4 = very much). Participants completed the questionnaire at screening and every other dose. Baseline is defined as the last value taken on or before the first dose of study drug administered in Week 37. Score is calculated by multiplying the sum of item scores by the n of items in the scale, then divided by n of items answered.

End point type	Secondary

End point timeframe:

Baseline and over a continuous 12 week period (from week 37 through week 48)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	47		
Units: Percent of Participants				
number (confidence interval 95%)	36.2 (26.5 to 46.7)	21.3 (10.7 to 35.7)		

Statistical analyses

Statistical analysis title	FACT-IF
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0657
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	5.4

Secondary: Percentage of Participants With Improvement of Iron Overload

End point title	Percentage of Participants With Improvement of Iron Overload

End point description:

Iron overload was measured by Liver Iron Concentration (LIC) and Iron Chelation Therapy (ICT) daily dose. Improvement is defined as: - For participants with baseline LIC ≥3 mg/g: ≥20% reduction in LIC or ≥ 33% decrease in ICT daily dose - For participants with baseline LIC <3 mg/g: no increase in LIC >1 mg/g and not starting treatment with ICT, or no increase in ICT daily dose ≥ 33% (if on ICT at baseline)

End point type	Secondary

End point timeframe:

Week 24 and Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percent of participants				
number (not applicable)				
Week 24	44.8	49.0		
Week 48	34.4	49.0		

Statistical analyses

Statistical analysis title	LIC/ICT
Statistical analysis description:	
Percentage of participants with improvement of iron overload (LIC/ICT responders) at Week 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4787
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.4
upper limit	13

Statistical analysis title	LIC/ICT
Statistical analysis description:	
Percentage of participants with improvement of iron overload (LIC/ICT responders) at Week 48	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0827
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	2.4

Secondary: Mean Change From Baseline in Serum Ferritin

End point title	Mean Change From Baseline in Serum Ferritin

End point description:

Baseline mean serum ferritin is calculated during the 24 weeks on or prior to dose 1 day 1. Post-

baseline mean serum ferritin is calculated as mean of ferritin values during the last 24 weeks on or prior to the end date of the first 24 week or 48 week treatment

End point type	Secondary

End point timeframe:

Week 24 and Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	44		
Units: ug/L				
least squares mean (standard error)				
Week 24	29.32 (± 22.949)	2.18 (± 32.217)		
Week 48	84.94 (± 23.120)	71.48 (± 32.457)		

Statistical analyses

Statistical analysis title	Serum Ferritin

Statistical analysis description:

Mean change from baseline in serum ferritin at Week 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3454
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	13.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.01
upper limit	87.93

Statistical analysis title	Serum Ferritin

Statistical analysis description:

Mean change from baseline in serum ferritin at Week 24

Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5949
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	27.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.77
upper limit	101.06

Secondary: Mean Change From Baseline in Liver Iron Concentration (LIC)

End point title	Mean Change From Baseline in Liver Iron Concentration (LIC)

End point description:

LIC was measured by Magnetic Resonance Imaging (MRI). Baseline is defined as the last value on or before the first dose of study drug is administered; Postbaseline is defined as the closest visit at Week 24 or Week 48. Participants with LIC value >43 are not included in the analysis.

End point type	Secondary

End point timeframe:

Week 24 and Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	45		
Units: mg/g dry weight				
least squares mean (standard error)				
Week 24	-0.30 (± 0.125)	-0.21 (± 0.169)		
Week 48	-0.34 (± 0.233)	-1.00 (± 0.329)		

Statistical analyses

Statistical analysis title	LIC

Statistical analysis description:

Mean change from baseline in LIC at Week 48

Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0859
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	1.42

Statistical analysis title	LIC
Statistical analysis description:	
Mean change from baseline in LIC at Week 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6628
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.3

Secondary: Percentage of Participants Who are Transfusion-Free Over 48 Weeks

End point title	Percentage of Participants Who are Transfusion-Free Over 48 Weeks
End point description:	
Transfusion free is defined as the absence of any transfusion during Week 1-48 of study treatment. Participants who discontinued treatment prior to Week 48 were not considered as transfusion free during Week 1-48.	
End point type	Secondary
End point timeframe:	
From first dose to Week 48	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percent of Participants				
number (not applicable)	82.3	44.9		

Statistical analyses

Statistical analysis title	Transfusion-Free

Statistical analysis description:

Percentage of Participants Who are Transfusion-Free Over 48 Weeks

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	37.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.9
upper limit	53

Secondary: Percentage of Participants Who are Transfusion-Free Over 24 Weeks

End point title	Percentage of Participants Who are Transfusion-Free Over 24 Weeks

End point description:

Transfusion free is defined as the absence of any transfusion during Week 1-24 of study treatment. Participants who discontinued treatment prior to Week 24 were not considered as transfusion free during Week 1-24.

End point type	Secondary

End point timeframe:

From first dose to Week 24

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percent of Participants				
number (not applicable)	89.6	67.3		

Statistical analyses

Statistical analysis title	Tranfusion Free
Statistical analysis description:	
Percentage of participants who were transfusion free over 24 weeks	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	22.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	38.6

Secondary: Duration of the Mean Hemoglobin Increase From Baseline ≥1.0 g/dL

End point title	Duration of the Mean Hemoglobin Increase From Baseline ≥1.0 g/dL
End point description:	
This outcome measure is the cumulative mean of the duration of hemoglobin response for the ≥ 1.0 g/dL during any 12-week rolling period. Any hemoglobin values within 21 days after a transfusion were excluded from the analysis.	
End point type	Secondary
End point timeframe:	
From baseline up to approximately 56 months	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	11		
Units: Days				
arithmetic mean (standard deviation)	1136.0 (± 491.86)	203.3 (± 170.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the 6-Minute Walk Test (6MWT) Distance

End point title	Mean Change From Baseline in the 6-Minute Walk Test (6MWT) Distance

End point description:

The 6MWT is typically used to objectively assess functional exercise capacity and response to medical interventions in patients with various moderate to severe diseases. Particiapnts are asked to walk as quickly as possible without running along a 30-meter corridor for six minutes, and the total distance covered during that time is measured. Baseline is defined as the last value on or before the first dose of study drug is administered. Postbaseline is defined as the closest visit at Week 24 or Week 48.

End point type	Secondary

End point timeframe:

From baseline to Week 24 and from baseline to Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	47		
Units: Meters				
least squares mean (standard error)				
24 Weeks	7.20 (± 7.017)	-8.96 (± 9.297)		
48 Weeks	8.82 (± 5.907)	-3.62 (± 8.141)		

Statistical analyses

Statistical analysis title	6MWT

Statistical analysis description:

Mean change from baseline in 6MWT distance at Week 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2011
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	12.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.72
upper limit	31.59

Statistical analysis title	6MWT

Statistical analysis description:	
Mean change from baseline in 6MWT distance at Week 24	
Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1466
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	16.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	38.04

Secondary: Percentage of Participants with an Increase From Baseline ≥1.5 g/dL in Mean Hemoglobin Values in the Absence of Transfusion

End point title	Percentage of Participants with an Increase From Baseline ≥1.5 g/dL in Mean Hemoglobin Values in the Absence of Transfusion
End point description:	
Percentage of participants who have an increase from baseline ≥1.5 g/dL in mean of hemoglobin (Hb) values over a continuous 12-week interval from Week 13 to Week 24 in the absence of transfusions. Baseline was defined as the average of 2 or more Hb measurements at least 1 week apart within 4 weeks before Dose 1 Day 1.	
End point type	Secondary
End point timeframe:	
From Week 13 to Week 24 of study treatment	

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percentage of Participants				
number (confidence interval 95%)	52.1 (41.6 to 62.4)	0.0 (0.0 to 7.3)		

Statistical analyses

Statistical analysis title	Hemoglobin Values
Statistical analysis description:	
Percentage of Participants with an Increase From Baseline ≥1.5 g/dL in Mean Hemoglobin Values in the Absence of Transfusion	
Comparison groups	Luspatercept v Placebo

Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	52.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.2
upper limit	66.2

Secondary: Percentage of Participants With a Decrease From Baseline ≥ RD (= 1) in the Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score

End point title	Percentage of Participants With a Decrease From Baseline ≥ RD (= 1) in the Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score

End point description:

The responder definition (RD) threshold is the individual participant score change over a predetermined time period that will be interpreted as a treatment benefit. The RD for the NTDT-PRO T/W domain score was defined as ≥ 1-point decrease (ie, RD = -1) from baseline over the time from Week 13 to Week 24 or from Week 37 to Week 48. Participants with missing NTDT-PRO T/W scores at the indicated 12-week period are classified as non-responders in the analysis.

End point type	Secondary

End point timeframe:

From Week 13 to Week 24 and from Week 37 to Week 48 of study treatment

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Percent of participants				
number (confidence interval 95%)				
Week 13 to week 24	37.5 (27.8 to 48.0)	28.6 (16.6 to 43.3)		
Week 37 to week 48	31.3 (22.2 to 41.5)	18.4 (8.8 to 32.0)		

Statistical analyses

Statistical analysis title	NTDT-PRO

Statistical analysis description:

Percentage of Participants With a Decrease From Baseline ≥ RD (= 1) in the Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score Week 37 to Week 48

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0733
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	5

Statistical analysis title	NTDT-PRO

Statistical analysis description:

Percentage of Participants With a Decrease From Baseline ≥ RD (= 1) in the Non-Transfusion Dependent β-thalassemia-Patient Reported Outcome (NTDT-PRO) Tiredness and Weakness (T/W) Domain Score Week 13 to Week 24

Comparison groups	Luspatercept v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1989
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	3.7

Secondary: Number of Participants Experiencing Adverse Events

End point title	Number of Participants Experiencing Adverse Events

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. Adverse events are graded on a scale from 1 to 5, with Grade 1 being mild and asymptomatic; Grade 2 is moderate requiring minimal, local or noninvasive intervention; Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 events are usually severe enough to require hospitalization; Grade 5 events are fatal.

End point type	Secondary

End point timeframe:

From first dose to 63 days after last dose (up to approximately 56 months)

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Participants				
Treatment-emergent adverse-event (TEAE)	96	48		
Serious TEAE	23	13		
Treatment-related TEAE	79	18		
Treatment-related Serious TEAE	4	0		
TEAE Leading to Death	1	0		
TEAE Leading to Dose Reduction	11	0		
TEAE Leading to Dose Delay	47	11		
TEAE Leading to Study Drug Discontinuation	5	4		
Treatment-related TEAE Leading to Death	0	0		
Treatment-related TEAE Leading to Dose Reduction	11	0		
Treatment-related TEAE Leading to Dose Delay	10	0		
Treatment-related TEAE Study Drug Discontinuation	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-drug Antibody (ADA) Positive Test for Luspatercept

End point title	Number of Participants with Anti-drug Antibody (ADA) Positive Test for Luspatercept

End point description:

Presence of anti-drug (ACE-536/Luspatercept) antibodies was assessed every 24 weeks from serum samples. A participant is counted as 'positive' if there is any positive result captured during the study.

End point type	Secondary

End point timeframe:

From first dose and up to 2 years following last dose, up to approximately 56 months

End point values	Luspatercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	49		
Units: Participants	5	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Luspatercept

End point title	Apparent Clearance (CL/F) of Luspatercept[1]

End point description:

Apparent Clearance (CL/F) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: L/day				
geometric mean (geometric coefficient of variation)	0.458 (± 33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution of the Central Compartment (V1/F) of Luspatercept

End point title	Apparent Volume of Distribution of the Central Compartment (V1/F) of Luspatercept[2]

End point description:

Apparent Volume of Distribution of the Central Compartment (V1/F) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Liters				
geometric mean (geometric coefficient of variation)	7.79 (± 19.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Luspatercept

End point title	Maximum Concentration (Cmax) of Luspatercept[3]

End point description:

Maximum Concentration (Cmax) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	5.55 (± 16.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration From Steady State (Cmax,ss) of Luspatercept

End point title	Maximum Concentration From Steady State (Cmax,ss) of Luspatercept[4]

End point description:

Maximum Concentration From Steady State (Cmax,ss) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	8.36 (± 27.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Steady State (AUCss) of Luspatercept

End point title	Area Under the Curve From Steady State (AUCss) of Luspatercept[5]

End point description:

Area Under the Curve From Steady State (AUCss) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: day*µg/mL				
geometric mean (geometric coefficient of variation)	130 (± 34.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) of Luspatercept

End point title	Time to Reach Maximum Concentration (Tmax) of

End point description:

Time to Reach Maximum Concentration (Tmax) of Luspatercept

End point type	Secondary

End point timeframe:

Doses 1 to 16: at predose (must be collected before first dose), Dose 2 Day 1, Dose 4 Day 1, Dose 6 Day 1, Dose 8 Day 1, Dose 12 Day 1, Dose 16 Day 1, Dose 6 Day 8, Dose 6 Day 15, and every 6 doses (at Dose 22, 28, etc.), up to approx. 48 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic data can not be assessed for the placebo arm. Thus, no data was evaluate for the placebo arm, nor was it ever planned to be according to the protocol

End point values	Luspatercept			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Days				
median (full range (min-max))	5.50 (4.33 to 6.42)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to 63 days after last dose (up to approximately 56 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Luspatercept

Reporting group description:

Luspatercept was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle). The starting dose level was 1.00 mg/kg and could be escalated to 1.25 mg/kg and/or reduced to 0.80, 0.60, and
0.45 mg/kg. Participants were treated for a minimum of 48 weeks.

Reporting group title	Placebo-Luspatercept

Reporting group description:

Open-label phase in which participants switched from placebo and started Luspatercept treatment for up to approximately 24 months.

Reporting group title	Placebo

Reporting group description:

Placebo (0.9% sodium chloride for injection) was administered as subcutaneous injection once every 3 weeks (administered on Study Day 1 of each 21-day treatment cycle) for a minimum of 48 weeks. Eligible participants entered an open-label phase and started Luspatercept treatment for up to approximately 24 months.

Serious adverse events	Luspatercept	Placebo-Luspatercept	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 96 (23.96%)	3 / 38 (7.89%)	13 / 49 (26.53%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 96 (0.00%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 96 (0.00%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic obstruction			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	2 / 96 (2.08%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary contusion			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Traumatic fracture			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular hypokinesia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenomegaly			

subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extramedullary haemopoiesis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 96 (2.08%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue haemorrhagic fever			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal disease			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Steroid diabetes			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Luspatercept	Placebo-Luspatercept	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 96 (100.00%)	38 / 38 (100.00%)	48 / 49 (97.96%)
Vascular disorders			
Prehypertension			
subjects affected / exposed	23 / 96 (23.96%)	3 / 38 (7.89%)	7 / 49 (14.29%)
occurrences (all)	39	3	10
Hypertension			
subjects affected / exposed	21 / 96 (21.88%)	7 / 38 (18.42%)	1 / 49 (2.04%)
occurrences (all)	45	7	1
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	6 / 96 (6.25%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	8	1	1
Injection site erythema			
subjects affected / exposed	5 / 96 (5.21%)	3 / 38 (7.89%)	0 / 49 (0.00%)
occurrences (all)	6	14	0
Influenza like illness			
subjects affected / exposed	25 / 96 (26.04%)	2 / 38 (5.26%)	3 / 49 (6.12%)
occurrences (all)	38	2	3

Fatigue			
subjects affected / exposed	23 / 96 (23.96%)	8 / 38 (21.05%)	10 / 49 (20.41%)
occurrences (all)	26	10	12
Asthenia			
subjects affected / exposed	19 / 96 (19.79%)	0 / 38 (0.00%)	5 / 49 (10.20%)
occurrences (all)	34	0	8
Oedema peripheral			
subjects affected / exposed	6 / 96 (6.25%)	1 / 38 (2.63%)	2 / 49 (4.08%)
occurrences (all)	10	1	2
Pyrexia			
subjects affected / exposed	30 / 96 (31.25%)	11 / 38 (28.95%)	9 / 49 (18.37%)
occurrences (all)	49	17	9
Pain			
subjects affected / exposed	4 / 96 (4.17%)	2 / 38 (5.26%)	0 / 49 (0.00%)
occurrences (all)	4	2	0
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	18 / 96 (18.75%)	5 / 38 (13.16%)	0 / 49 (0.00%)
occurrences (all)	25	6	0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	3 / 96 (3.13%)	3 / 38 (7.89%)	1 / 49 (2.04%)
occurrences (all)	3	3	1
Menstruation irregular			
subjects affected / exposed	13 / 96 (13.54%)	2 / 38 (5.26%)	3 / 49 (6.12%)
occurrences (all)	29	2	4
Dysmenorrhoea			
subjects affected / exposed	8 / 96 (8.33%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	38	1	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 96 (5.21%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences (all)	8	1	0
Cough			
subjects affected / exposed	24 / 96 (25.00%)	2 / 38 (5.26%)	1 / 49 (2.04%)
occurrences (all)	39	2	1

Rhinorrhoea			
subjects affected / exposed	4 / 96 (4.17%)	1 / 38 (2.63%)	3 / 49 (6.12%)
occurrences (all)	5	1	3
Rhinitis allergic			
subjects affected / exposed	7 / 96 (7.29%)	0 / 38 (0.00%)	3 / 49 (6.12%)
occurrences (all)	10	0	3
Pulmonary hypertension			
subjects affected / exposed	0 / 96 (0.00%)	2 / 38 (5.26%)	2 / 49 (4.08%)
occurrences (all)	0	2	2
Pleuritic pain			
subjects affected / exposed	0 / 96 (0.00%)	2 / 38 (5.26%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	23 / 96 (23.96%)	1 / 38 (2.63%)	6 / 49 (12.24%)
occurrences (all)	34	1	10
Epistaxis			
subjects affected / exposed	12 / 96 (12.50%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	20	1	5
Nasal congestion			
subjects affected / exposed	8 / 96 (8.33%)	1 / 38 (2.63%)	2 / 49 (4.08%)
occurrences (all)	12	1	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 96 (14.58%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	20	1	1
Anxiety			
subjects affected / exposed	10 / 96 (10.42%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences (all)	10	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	6	0	3
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	5	0	0

Ligament sprain			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	5	0	0
Fall			
subjects affected / exposed	2 / 96 (2.08%)	3 / 38 (7.89%)	0 / 49 (0.00%)
occurrences (all)	3	3	0
Traumatic fracture			
subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	6	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	9 / 96 (9.38%)	4 / 38 (10.53%)	6 / 49 (12.24%)
occurrences (all)	14	4	6
Tachycardia			
subjects affected / exposed	6 / 96 (6.25%)	2 / 38 (5.26%)	2 / 49 (4.08%)
occurrences (all)	6	3	3
Nervous system disorders			
Sciatica			
subjects affected / exposed	5 / 96 (5.21%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences (all)	6	1	0
Dizziness			
subjects affected / exposed	19 / 96 (19.79%)	3 / 38 (7.89%)	4 / 49 (8.16%)
occurrences (all)	26	3	4
Headache			
subjects affected / exposed	44 / 96 (45.83%)	10 / 38 (26.32%)	10 / 49 (20.41%)
occurrences (all)	175	17	20
Migraine			
subjects affected / exposed	9 / 96 (9.38%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	22	0	0
Blood and lymphatic system disorders			
Extramedullary haemopoiesis			
subjects affected / exposed	9 / 96 (9.38%)	2 / 38 (5.26%)	2 / 49 (4.08%)
occurrences (all)	9	3	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 96 (3.13%)	0 / 38 (0.00%)	4 / 49 (8.16%)
occurrences (all)	3	0	5

Vertigo			
subjects affected / exposed	3 / 96 (3.13%)	0 / 38 (0.00%)	3 / 49 (6.12%)
occurrences (all)	4	0	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	15 / 96 (15.63%)	5 / 38 (13.16%)	3 / 49 (6.12%)
occurrences (all)	22	8	3
Abdominal pain			
subjects affected / exposed	18 / 96 (18.75%)	4 / 38 (10.53%)	5 / 49 (10.20%)
occurrences (all)	20	5	6
Dyspepsia			
subjects affected / exposed	18 / 96 (18.75%)	3 / 38 (7.89%)	2 / 49 (4.08%)
occurrences (all)	20	3	2
Dental caries			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	2 / 49 (4.08%)
occurrences (all)	5	0	2
Diarrhoea			
subjects affected / exposed	25 / 96 (26.04%)	5 / 38 (13.16%)	6 / 49 (12.24%)
occurrences (all)	43	9	7
Vomiting			
subjects affected / exposed	11 / 96 (11.46%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	12	1	1
Toothache			
subjects affected / exposed	15 / 96 (15.63%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	22	0	1
Nausea			
subjects affected / exposed	14 / 96 (14.58%)	1 / 38 (2.63%)	6 / 49 (12.24%)
occurrences (all)	21	1	11
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	3 / 49 (6.12%)
occurrences (all)	5	0	3
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	6	0	0
Skin and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	7 / 96 (7.29%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	15	1	1
Pruritus			
subjects affected / exposed	3 / 96 (3.13%)	2 / 38 (5.26%)	0 / 49 (0.00%)
occurrences (all)	3	2	0
Erythema			
subjects affected / exposed	7 / 96 (7.29%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences (all)	7	2	0
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	1 / 96 (1.04%)	0 / 38 (0.00%)	3 / 49 (6.12%)
occurrences (all)	1	0	3
Dysuria			
subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	8	0	1
Albuminuria			
subjects affected / exposed	2 / 96 (2.08%)	2 / 38 (5.26%)	0 / 49 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	37 / 96 (38.54%)	11 / 38 (28.95%)	8 / 49 (16.33%)
occurrences (all)	82	19	15
Back pain			
subjects affected / exposed	38 / 96 (39.58%)	14 / 38 (36.84%)	6 / 49 (12.24%)
occurrences (all)	77	29	7
Bone pain			
subjects affected / exposed	42 / 96 (43.75%)	8 / 38 (21.05%)	3 / 49 (6.12%)
occurrences (all)	103	13	3
Muscle spasms			
subjects affected / exposed	3 / 96 (3.13%)	2 / 38 (5.26%)	1 / 49 (2.04%)
occurrences (all)	4	3	1
Muscular weakness			
subjects affected / exposed	3 / 96 (3.13%)	1 / 38 (2.63%)	3 / 49 (6.12%)
occurrences (all)	3	1	4
Musculoskeletal chest pain			

subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	8	0	1
Musculoskeletal pain			
subjects affected / exposed	6 / 96 (6.25%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	6	1	1
Myalgia			
subjects affected / exposed	16 / 96 (16.67%)	3 / 38 (7.89%)	5 / 49 (10.20%)
occurrences (all)	25	5	5
Neck pain			
subjects affected / exposed	12 / 96 (12.50%)	1 / 38 (2.63%)	2 / 49 (4.08%)
occurrences (all)	17	1	4
Osteoporosis			
subjects affected / exposed	6 / 96 (6.25%)	1 / 38 (2.63%)	0 / 49 (0.00%)
occurrences (all)	6	1	0
Pain in extremity			
subjects affected / exposed	29 / 96 (30.21%)	6 / 38 (15.79%)	5 / 49 (10.20%)
occurrences (all)	47	8	6
Pain in jaw			
subjects affected / exposed	1 / 96 (1.04%)	3 / 38 (7.89%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Spinal pain			
subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	8	0	1
Tendonitis			
subjects affected / exposed	5 / 96 (5.21%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	6	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 96 (6.25%)	1 / 38 (2.63%)	1 / 49 (2.04%)
occurrences (all)	6	1	1
COVID-19			
subjects affected / exposed	34 / 96 (35.42%)	15 / 38 (39.47%)	0 / 49 (0.00%)
occurrences (all)	36	15	0
Gastroenteritis			
subjects affected / exposed	12 / 96 (12.50%)	2 / 38 (5.26%)	2 / 49 (4.08%)
occurrences (all)	15	2	3

Helicobacter infection			
subjects affected / exposed	0 / 96 (0.00%)	2 / 38 (5.26%)	0 / 49 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	15 / 96 (15.63%)	1 / 38 (2.63%)	5 / 49 (10.20%)
occurrences (all)	18	1	7
Nasopharyngitis			
subjects affected / exposed	7 / 96 (7.29%)	0 / 38 (0.00%)	0 / 49 (0.00%)
occurrences (all)	10	0	0
Pharyngitis			
subjects affected / exposed	21 / 96 (21.88%)	1 / 38 (2.63%)	6 / 49 (12.24%)
occurrences (all)	30	1	13
Rhinitis			
subjects affected / exposed	9 / 96 (9.38%)	0 / 38 (0.00%)	6 / 49 (12.24%)
occurrences (all)	11	0	6
Sinusitis			
subjects affected / exposed	4 / 96 (4.17%)	2 / 38 (5.26%)	1 / 49 (2.04%)
occurrences (all)	7	2	1
Tonsillitis			
subjects affected / exposed	4 / 96 (4.17%)	1 / 38 (2.63%)	6 / 49 (12.24%)
occurrences (all)	5	2	7
Tooth abscess			
subjects affected / exposed	6 / 96 (6.25%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	9	0	1
Upper respiratory tract infection			
subjects affected / exposed	23 / 96 (23.96%)	1 / 38 (2.63%)	11 / 49 (22.45%)
occurrences (all)	42	1	32
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	5 / 96 (5.21%)	0 / 38 (0.00%)	1 / 49 (2.04%)
occurrences (all)	5	0	1
Hyperuricaemia			
subjects affected / exposed	8 / 96 (8.33%)	1 / 38 (2.63%)	2 / 49 (4.08%)
occurrences (all)	9	1	2
Iron overload			

subjects affected / exposed	14 / 96 (14.58%)	0 / 38 (0.00%)	5 / 49 (10.20%)
occurrences (all)	15	0	5
Vitamin D deficiency			
subjects affected / exposed	9 / 96 (9.38%)	2 / 38 (5.26%)	4 / 49 (8.16%)
occurrences (all)	11	2	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2018	Added additional criteria for dose modification; description of TRV and EMH masses measurements have been clarified for consistency; exclusion criterion clarified.
12 June 2020	Open-Label Phase (OLP) added to study design; modification to PRO Minimum Clinical Important Difference (MCID) and Responder Definition (RD)Thresholds); Table of Events, Treatment Schedule and Procedures was updated to include the OLP; rationale for the key secondary endpoints were updated; clarified use of the Quality of Life questionnaire; monitoring of thromboembolic events has been added as event of interest; correction of typos.
27 April 2022	Updated morbidity-free parameters; changed open-label duration; added COVID-19 guidelines; modify medical monitor; added modification of monitoring extramedullary masses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported