



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 31 December 2022 |
| First version publication date | 05 December 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ACE-536-MDS-001 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 November 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 45 |
| From 65 to 84 years | 174 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

229 participants were randomized and treated.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------|
| Arm title | Luspatercept |
|------------------|--------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

Volume equivalent to experimental arm, subcutaneously injection every 3 weeks

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

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

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

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

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

| | |
|---|---|
| End point title | Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) \geq 12 Weeks From Week 1 to Week 24 |
| End point description: RBC-TI Response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 24 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: From Week 1 through Week 24 of study treatment | |

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

Statistical analyses

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

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

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

| | |
|---|---|
| End point title | Percentage of Participants Who Achieved Red Blood Cell Transfusion Independence (RBC-TI) \geq 12 Weeks From Week 1 to Week 48 |
| End point description: RBC-TI Response was defined as the absence of any Red Blood Cells (RBC) transfusion during any consecutive 84-day (12-week) period (ie, Days 1 to 84, Days 2 to 85, Days 3 to 86, etc.) during the first 48 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: From Week 1 through Week 48 of study treatment | |

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

Statistical analyses

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

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Week 1 through Week 48 of study treatment

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

Statistical analyses

| Statistical analysis title | RBC-TI ≥ 8 weeks_3 |
|---|---|
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Risk Difference on Response Rate |
| Point estimate | 29.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.73 |
| upper limit | 40.36 |

| Statistical analysis title | RBC-TI ≥ 8 weeks_4 |
|---|-------------------------|
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.306 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.526 |
| upper limit | 11.146 |

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

| | |
|---|--|
| End point title | Change From Baseline in RBC Units Transfused Over Fixed 16-Week Period |
| End point description: Mean change in total number of Red Blood Cells (RBC) units transfused over a fixed 16-week period (Week 9-24 or Week 33-48) from the total number of RBC units transfused in the 16 weeks immediately on or prior to first dose of study treatment. | |
| End point type | Secondary |
| End point timeframe: At Baseline (16 weeks prior to first dose of study treatment) and Weeks 9 to 24 or Weeks 33 to 48 | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--|
| End point title | Percentage of Participants who Achieved a Modified Hematologic Erythroid Response (mHI-E) Over any Consecutive 56-Day Period |
| End point description: A modified HI-E response was defined as the percentage of participants meeting the modified HI-E per the International Working Group (IWG) sustained over 56-day consecutive period during the Treatment period. For participants with a baseline RBC transfusion burden of ≥ 4 units/8 weeks, a mHI-E was defined as a reduction in RBC transfusion of at least 4 units/8 weeks; for participants with baseline RBC transfusion burden of <4 units/8 weeks, mHI-E, was defined as a mean increase in hemoglobin of ≥ 1.5 g/dL for 8 weeks in the absence of RBC transfusions. | |
| End point type | Secondary |
| End point timeframe: Week 1 through 24 or Week 1 Through Week 48 | |

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

Statistical analyses

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

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

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

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

End point description:

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

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

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 1 though Week 24 and Week 1 through 48 | |

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

Statistical analyses

| Statistical analysis title | Hgb increase_1 |
|---|------------------------|
| Statistical analysis description: | |
| Week 1 Through Week 24 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Fisher exact |

| Statistical analysis title | Hgb increase_2 |
|---|------------------------|
| Statistical analysis description: | |
| Week 1 Through Week 48 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Fisher exact |

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

| | |
|----------------------------|--------|
| Statistical analysis title | HI-N_1 |
|----------------------------|--------|

Statistical analysis description:

Week 1 -24

| | |
|---|-------------------------|
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2382 |
| Method | Cochran-Mantel-Haenszel |

| | |
|--|-------------------------|
| Statistical analysis title | HI-N_2 |
| Statistical analysis description: Week 1 - 48 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5127 |
| Method | Cochran-Mantel-Haenszel |

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

| | |
|---|--|
| End point title | Percentage of Participants who Achieved a Hematologic Improvement in Platelet Response (HI-P) Over any Consecutive 56-day Period |
| End point description: Percentage of participants who achieved a hematologic improvement platelet response (HI-P) was defined as the percentage of participants meeting the HI-P criteria per the IWG sustained over any consecutive 56-day (8-week) period (Week 1 to Week 24 and Week 1 to Week 48) during the treatment period. HI – P reponse was defined as: • Absolute increase of $\geq 30 \times 10^9/L$ in platelets for participants starting with $> 20 \times 10^9/L$ platelets • Increase in platelets from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100% | |
| End point type | Secondary |
| End point timeframe: Week 1 through Week 24 or Week 1 Through Week 48 of study treatment | |

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

Statistical analyses

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

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

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

Secondary: Change from Baseline in Mean Serum Ferritin

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

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

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Ferritin_1 |
| Statistical analysis description: Week 9 Through 24 | |
| Comparison groups | Luspatercept v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 222 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0024 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -229.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -375.8 |
| upper limit | -82.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 74.43 |

| | |
|---|----------------------------|
| Statistical analysis title | Ferritin_2 |
| Statistical analysis description: Week 33 Through 48 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 222 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0294 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -319.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -606.3 |
| upper limit | -32.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 144.57 |

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

| | |
|--|---|
| End point title | Change from Baseline in Mean Daily Dose of Iron Chelation Therapy (ICT) |
| End point description: Mean change from baseline in mean daily dose of ICT averaged over Week 9 to Week 24 or Week 33 to Week 48. For each participant, the mean change in daily dose of ICT was calculated as the difference of postbaseline mean daily dose and baseline mean daily dose. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 9 through Week 24 and Week 33 through Week 48 of study treatment | |

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

Statistical analyses

| Statistical analysis title | ICT_2 |
|--|----------------------------|
| Statistical analysis description: Weeks 33 Through 48 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7903 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -24.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -210.7 |
| upper limit | 160.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 93.42 |

| Statistical analysis title | ICT_1 |
|---|------------------------|
| Statistical analysis description: Weeks 9 Through 24 | |
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3087 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -41 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -120.3 |
| upper limit | 38.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 40.18 |

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

| | |
|--|---|
| End point title | Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 48 |
| End point description: Time to RBC-TI was defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 48 | |
| End point type | Secondary |
| End point timeframe: From first dose to Week 48 of study treatment | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Time to Red Blood Cell Transfusion Independence (RBC-TI) - Week 1 Through Week 24 |
| End point description: Time to RBC-TI was defined as the time between first dose date and the date of onset of RBC-TI first observed for participants who achieved RBC-TI of ≥ 8 weeks during Week 1 through Week 24 | |
| End point type | Secondary |
| End point timeframe: From first dose to Week 24 of study treatment | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Percentage of Participants who Progressed to Acute Myeloid Leukemia (AML) |
| End point description: Percentage of participants progressing to AML throughout the course of the study | |
| End point type | Secondary |
| End point timeframe: From randomization to study completion (up to approximately 57 months) | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Acute Myeloid Leukemia (AML) Progression

| | |
|--|--|
| End point title | Time to Acute Myeloid Leukemia (AML) Progression |
| End point description: Time to AML progression was defined as the time between randomization date and the first diagnosis of AML as per World Health Organization (WHO) classification of ≥ 20% blasts in peripheral blood or bone marrow. Participants with a diagnosis of AML were considered to have had an event, participants who did not progress to AML at the time of analysis were censored at the last assessment date which did not indicate progression to AML. Median was not reached because of insufficient number of events | |
| End point type | Secondary |
| End point timeframe: From randomization to study completion (up to approximately 57 months) | |

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

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

Statistical analyses

| Statistical analysis title | OS |
|---|------------------------|
| Comparison groups | Luspatercept v Placebo |
| Number of subjects included in analysis | 229 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.958 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.986 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.595 |
| upper limit | 1.636 |

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[4] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Apparent volume of distribution of luspatercept was calculated according to the equation $V_z = (CL)/\lambda$.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[5] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Luspatercept | Placebo | | |
|-------------------------------|---------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153 | 0 ^[6] | | |
| Units: Day | | | | |
| median (full range (min-max)) | 5.40 (3.12 to 6.69) | (to) | | |

Notes:

[6] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Terminal phase half-life was calculated according to the following equation: $t_{1/2} = 0.693/\lambda_z$.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Luspatercept | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153 | 0 ^[7] | | |
| Units: Day | | | | |
| geometric mean (geometric coefficient of variation) | 13.0 (± 31.6) | () | | |

Notes:

[7] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (C_{max}) at Steady State

| | |
|-----------------|---|
| End point title | Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the Starting Dose (C _{max}) at Steady State |
|-----------------|---|

End point description:

C_{max} was defined as the observed maximum plasma concentration, obtained directly from the observed concentration at a steady state.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Luspatercept | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153 | 0 ^[8] | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 9.17 (± 29.9) | () | | |

Notes:

[8] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the First Dose (C_{max})

| | |
|-----------------|--|
| End point title | Pharmacokinetic (PK) Parameters: Bayesian Estimate of Maximum Concentration for the First Dose (C _{max}) |
|-----------------|--|

End point description:

C_{max} was defined as the observed maximum plasma concentration, obtained directly from the observed concentration versus time.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Luspatercept | Placebo | | |
|---|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153 | 0 ^[9] | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 5.77 (± 20.5) | () | | |

Notes:

[9] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[10] - Subjects did not receive investigational drug product

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of participants with positive ADA prior to taking study drug and/or during study. A participant

was counted as "treatment-emergent" if there was a positive post-baseline sample while the baseline sample was ADA negative, or there was a positive post-baseline sample with a titer \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 |
| End point timeframe: | |
| From randomization to 1 year post first dose | |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo (Volume equivalent to experimental arm) SC on Day 1 of each 21-day treatment cycle. Placebo is with a median duration of treatment of 168 days

| | |
|-----------------------|--------------|
| Reporting group title | Luspatercept |
|-----------------------|--------------|

Reporting group description:

Luspatercept 1.0 mg/Kg SC on Day 1 of each 21-day treatment cycle. Luspatercept is with a median duration of treatment of 356 days

| Serious adverse events | Placebo | Luspatercept | |
|---|------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 76 (30.26%) | 66 / 153 (43.14%) | |
| number of deaths (all causes) | 24 | 45 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon adenoma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 3 / 153 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraductal papillary mucinous neoplasm | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Luspatercept | |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 63 / 76 (82.89%) | 145 / 153 (94.77%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 16 / 153 (10.46%) | |
| occurrences (all) | 8 | 53 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 76 (11.84%) | 40 / 153 (26.14%) | |
| occurrences (all) | 9 | 74 | |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 9 / 153 (5.88%) | |
| occurrences (all) | 4 | 11 | |
| Malaise | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 8 / 153 (5.23%) | |
| occurrences (all) | 3 | 11 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 19 / 153 (12.42%) | |
| occurrences (all) | 7 | 24 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 13 / 76 (17.11%) | 37 / 153 (24.18%) | |
| occurrences (all) | 14 | 45 | |
| Fatigue | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 11 / 76 (14.47%) 14 | 46 / 153 (30.07%) 70 | |
| Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 0 | 8 / 153 (5.23%) 8 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 6 10 / 76 (13.16%) 13 3 / 76 (3.95%) 3 6 / 76 (7.89%) 6 | 30 / 153 (19.61%) 39 35 / 153 (22.88%) 50 12 / 153 (7.84%) 13 6 / 153 (3.92%) 6 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 5 0 / 76 (0.00%) 0 4 / 76 (5.26%) 4 1 / 76 (1.32%) 1 | 9 / 153 (5.88%) 10 9 / 153 (5.88%) 10 13 / 153 (8.50%) 14 9 / 153 (5.88%) 9 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 76 (3.95%) 7 | 9 / 153 (5.88%) 17 | |

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported