

**Clinical trial results:**

A Phase 2 Multicenter, Randomized, Open Label, Multiple Dose Study of Intravenous and Subcutaneous Administration of Sotatercept (ACE-011) in Subjects with End-Stage Kidney Disease on Hemodialysis Switched from Erythropoiesis Stimulating Agents with Staggered Dose Group Escalation in Part 1 Followed by a Parallel Group, Active Controlled Study of Selected Dose(s) and Regimen(s) in Part 2: to Evaluate the Pharmacokinetics, Safety, Tolerability, Efficacy, Dosing Regimen, and Pharmacodynamics of Sotatercept

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-003788-23 |
| Trial protocol | BE PT GB DE ES |
| Global end of trial date | 22 August 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 06 September 2017 |
| First version publication date | 06 September 2017 |

Trial information**Trial identification**

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ACE-011-REN-002 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01999582 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 86 Morris Avenue, Summit, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com |
| Scientific contact | Ted Reiss, Celgene Corporation, 01 908-897-6546, treiss@celgene.com |
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 86 Morris Avenue, Summit, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, 01 888-266-1599, ClinicalTrialDisclosure@celgene.com |
| Scientific contact | Ted Reiss, CVP, Head of I&I Clinical R&D, Celgene Corporation, 01 908-897-6546, TReiss@celgene.com |

Notes:

Paediatric regulatory details

| | |
|---------------------------------------|----|
| Is trial part of an agreed paediatric | No |
|---------------------------------------|----|

| | |
|--|----|
| investigation plan (PIP) | |
| 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 | 08 December 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | |
| | Yes |
| Global end of trial date | 22 August 2016 |
| Was the trial ended prematurely? | Yes |
| Notes: | |

General information about the trial

Main objective of the trial:

Part 1 To determine the multiple dose pharmacokinetics, safety, and tolerability of IV and SQ dosing of sotatercept administered at each dose level. Part 2 To determine the safety and efficacy of the selected starting dose(s), route(s) of administration, and dose modification regimen(s) on maintenance of hemoglobin concentrations between baseline and the Evaluation Phase

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 30 September 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Germany: 19 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

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) | 31 |
| From 65 to 84 years | 19 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 23 study centers in Belgium, Germany, Portugal, Spain, and the United Kingdom

Pre-assignment

Screening details:

Subjects with end stage kidney disease (ESKD) on maintenance hemodialysis must have demonstrated a stable hemoglobin (hbg) response to erythropoiesis stimulating agents (ESAs) (hemoglobin ≥ 10 g/dL to ≤ 12 g/dL [≥ 100 g/L to ≤ 120 g/L]) and switched from their ESA to sotatercept.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (Up to Visit 14) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection |

Arm description:

Subjects received sotatercept at 0.1 mg/kg administered IV every 14 days for up to 8 doses to evaluate the Pharmacokinetic (PK) and safety of IV versus subcutaneous (SQ) dosing of sotatercept.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Sotatercept at 0.1 mg/kg administered IV every 14 days for up to 8 doses. to evaluate the PK and safety of IV versus SQ dosing of sotatercept

| | |
|------------------|---|
| Arm title | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection |
|------------------|---|

Arm description:

Subjects received sotatercept at 0.13 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Sotatercept at 0.13 mg/kg administered SC every 14 days for up to 8 doses.

| | |
|------------------|---|
| Arm title | Group 2: Sotatercept 0.2 mg/kg IV injection |
|------------------|---|

Arm description:

Subjects received sotatercept at 0.2 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Sotatercept 0.2 mg/kg administered IV every 14 days for up to 8 doses. to evaluate the PK and safety of IV versus SQ dosing of sotatercept

| | |
|------------------|--|
| Arm title | Group 2: Sotatercept 0.26 mg/kg SC injection |
|------------------|--|

Arm description:

Subjects received sotatercept at 0.26 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Sotatercept 0.26 mg/kg administered SC every 14 days for up to 8 doses.

| | |
|------------------|---|
| Arm title | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection |
|------------------|---|

Arm description:

Subjects received sotatercept at a starting dose of 0.1 mg/kg that could be increased up to 0.4 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Sotatercept dose started at 0.1 mg/kg that could be escalated in 0.1 mg/kg increments up to 0.4 mg/kg administered IV every 14 days for up to 8 doses based on dose escalation rules.

| | |
|------------------|---|
| Arm title | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection |
|------------------|---|

Arm description:

Subjects received sotatercept at 0.4 mg/kg that could be increased to 0.5 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | ACE-011 |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Sotatercept dose started at 0.4 mg/kg that could be escalated to 0.5 mg/kg based on dose escalation rules and administered SC every 14 days for up to 8 doses.

| Number of subjects in period 1 | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection |
|--------------------------------|--|---|---|
| | | | |
| Started | 7 | 7 | 9 |
| Completed | 4 | 4 | 3 |
| Not completed | 3 | 3 | 6 |
| Consent withdrawn by subject | - | - | - |
| Adverse event, non-fatal | - | - | 3 |
| Protocol violation | - | - | - |
| Miscellaneous | 1 | - | 3 |
| Lack of efficacy | 1 | 3 | - |
| Protocol deviation | 1 | - | - |

| Number of subjects in period 1 | Group 2: Sotatercept 0.26 mg/kg SC injection | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection |
|--------------------------------|--|--|--|
| | | | |
| Started | 9 | 12 | 6 |
| Completed | 6 | 10 | 3 |
| Not completed | 3 | 2 | 3 |
| Consent withdrawn by subject | 1 | - | - |
| Adverse event, non-fatal | - | 1 | - |
| Protocol violation | - | - | 1 |
| Miscellaneous | 1 | 1 | 2 |
| Lack of efficacy | 1 | - | - |
| Protocol deviation | - | - | - |

Baseline characteristics

Reporting groups

| | |
|------------------------------|--|
| Reporting group title | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection |
| Reporting group description: | Subjects received sotatercept at 0.1 mg/kg administered IV every 14 days for up to 8 doses to evaluate the Pharmacokinetic (PK) and safety of IV versus subcutaneous (SQ) dosing of sotatercept. |
| Reporting group title | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection |
| Reporting group description: | Subjects received sotatercept at 0.13 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. |
| Reporting group title | Group 2: Sotatercept 0.2 mg/kg IV injection |
| Reporting group description: | Subjects received sotatercept at 0.2 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. |
| Reporting group title | Group 2: Sotatercept 0.26 mg/kg SC injection |
| Reporting group description: | Subjects received sotatercept at 0.26 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. |
| Reporting group title | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection |
| Reporting group description: | Subjects received sotatercept at a starting dose of 0.1 mg/kg that could be increased up to 0.4 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. |
| Reporting group title | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection |
| Reporting group description: | Subjects received sotatercept at 0.4 mg/kg that could be increased to 0.5 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. |

| Reporting group values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection |
|---------------------------------------|--|---|---|
| Number of subjects | 7 | 7 | 9 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 5 | 4 | 6 |
| From 65-84 years | 2 | 3 | 3 |
| Age continuous Units: years | | | |
| arithmetic mean | 59.1 | 62.3 | 59.4 |
| standard deviation | ± 15.43 | ± 13.03 | ± 15.8 |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 3 | 4 |
| Male | 3 | 4 | 5 |
| Race Units: Subjects | | | |
| White | 4 | 5 | 6 |
| Black or African- American | 1 | 1 | 1 |
| Asian | 2 | 0 | 2 |
| American Indian/Alaska Native | 0 | 1 | 0 |

| | | | |
|------------------------|---------|---------|---------|
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 1 |
| Not Hispanic or Latino | 7 | 6 | 8 |
| Frequency of dialysis | | | |
| Units: Subjects | | | |
| Once weekly | 0 | 0 | 0 |
| Twice weekly | 0 | 0 | 0 |
| Three times weekly | 7 | 7 | 8 |
| Four times weekly | 0 | 0 | 1 |
| Once daily | 0 | 0 | 0 |
| Duration of dialysis | | | |
| Units: minutes | | | |
| arithmetic mean | 284.3 | 262.1 | 241.6 |
| standard deviation | ± 26.99 | ± 27.97 | ± 33.34 |

| Reporting group values | Group 2: Sotatercept 0.26 mg/kg SC injection | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection |
|-------------------------------|--|--|--|
| Number of subjects | 9 | 12 | 6 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 4 | 8 | 4 |
| From 65-84 years | 5 | 4 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.9 | 61.4 | 53.7 |
| standard deviation | ± 15.43 | ± 15.68 | ± 15.93 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 5 | 3 |
| Male | 6 | 7 | 3 |
| Race | | | |
| Units: Subjects | | | |
| White | 8 | 11 | 6 |
| Black or African- American | 0 | 1 | 0 |
| Asian | 1 | 0 | 0 |
| American Indian/Alaska Native | 0 | 0 | 0 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 9 | 12 | 6 |
| Frequency of dialysis | | | |
| Units: Subjects | | | |
| Once weekly | 0 | 0 | 0 |
| Twice weekly | 0 | 1 | 0 |
| Three times weekly | 9 | 11 | 6 |
| Four times weekly | 0 | 0 | 0 |
| Once daily | 0 | 0 | 0 |

| | | | |
|---|------------------|------------------|----------------|
| Duration of dialysis Units: minutes arithmetic mean standard deviation | 255.8 ± 25.67 | 250.7 ± 18.09 | 259 ± 23.45 |
| Reporting group values | Total | | |
| Number of subjects | 50 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 31 | | |
| From 65-84 years | 19 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 22 | | |
| Male | 28 | | |
| Race Units: Subjects | | | |
| White | 40 | | |
| Black or African- American | 4 | | |
| Asian | 5 | | |
| American Indian/Alaska Native | 1 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 2 | | |
| Not Hispanic or Latino | 48 | | |
| Frequency of dialysis Units: Subjects | | | |
| Once weekly | 0 | | |
| Twice weekly | 1 | | |
| Three times weekly | 48 | | |
| Four times weekly | 1 | | |
| Once daily | 0 | | |
| Duration of dialysis Units: minutes arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection |
| Reporting group description: Subjects received sotatercept at 0.1 mg/kg administered IV every 14 days for up to 8 doses to evaluate the Pharmacokinetic (PK) and safety of IV versus subcutaneous (SQ) dosing of sotatercept. | |
| Reporting group title | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection |
| Reporting group description: Subjects received sotatercept at 0.13 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. | |
| Reporting group title | Group 2: Sotatercept 0.2 mg/kg IV injection |
| Reporting group description: Subjects received sotatercept at 0.2 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. | |
| Reporting group title | Group 2: Sotatercept 0.26 mg/kg SC injection |
| Reporting group description: Subjects received sotatercept at 0.26 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. | |
| Reporting group title | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection |
| Reporting group description: Subjects received sotatercept at a starting dose of 0.1 mg/kg that could be increased up to 0.4 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. | |
| Reporting group title | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection |
| Reporting group description: Subjects received sotatercept at 0.4 mg/kg that could be increased to 0.5 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept. | |

Primary: Area Under the Serum Concentration-Time Curve Over Dosing Interval (AUC14d) (14 days)

| | |
|---|--|
| End point title | Area Under the Serum Concentration-Time Curve Over Dosing Interval (AUC14d) (14 days) ^[1] |
| End point description: Area Under the plasma concentration-time curve Over 14-day dosing interval (AUC14) for Sotatercept., The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized. | |
| End point type | Primary |
| End point timeframe: Day 1 predose and postdose at 5 min, 4 hours, 3, 7 and dose 2 pre-dose. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 7 | 6 |
| Units: day*ng/mL | | | | |
| arithmetic mean (standard deviation) | 15204.31 (± 7096.55) | 11269.14 (± 1839.92) | 28647.03 (± 10332.19) | 10327.98 (± 8065.12) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 5 | | |
| Units: day*ng/mL | | | | |
| arithmetic mean (standard deviation) | 15886.83 (± 4212.12) | 21982.9 (± 5125.4) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Area under the serum concentration- time curve over from Day 1 to Day 28 (AUC28d)

| | |
|-----------------|--|
| End point title | Area under the serum concentration- time curve over from Day 1 to Day 28 (AUC28d) ^[2] |
|-----------------|--|

End point description:

Area under the plasma concentration-time curve Over 28-day dosing interval (AUC28d). The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Doses 1-2: predose and postdose (5 min, 4 hours, 3 and 7 days after each dose) and dose 3 predose.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 3 | 4 |
| Units: day*ng/mL | | | | |
| arithmetic mean (standard deviation) | 38361.5 (± 8589.34) | 41500.36 (± 13647.28) | 94106.54 (± 37204.17) | 36065.09 (± 22817) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: day*ng/mL | | | | |
| arithmetic mean (standard deviation) | 33173.4 (± 8709.16) | 60497.8 (± 14623.13) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Serum Concentration Obtained From the First Dose (Cmax14d)

| | |
|-----------------|--|
| End point title | Maximum Observed Serum Concentration Obtained From the First Dose (Cmax14d) ^[3] |
|-----------------|--|

End point description:

Maximum observed serum concentration (Cmax14d) of sotatercept, obtained directly from the observed concentration-time data. The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Dose 1: predose and postdose at 5 min, 4 hours, 3 and 7 days and dose 2 predose.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 8 | 6 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 2567.6 (± 1093.73) | 1024.27 (± 145.8) | 4623.61 (± 1620.66) | 963.05 (± 659.65) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 5 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 3155.53 (± 1861.07) | 1993.58 (± 375.54) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Serum Concentration (C_{max}28d) Obtained From the Combined First 2 Doses

| | |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (C _{max} 28d) Obtained From the Combined First 2 Doses ^[4] |
|-----------------|---|

End point description:

Maximum observed serum concentration (C_{max}28d) of sotatercept, obtained directly from the observed concentration-time data combining the profiles following the first two doses. The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Doses 1-2 predose and postdose at 5 min, 4 hours, 3 and 7 days after each dose and dose 3 predose.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 3 | 4 |
| Units: mg/mL | | | | |
| arithmetic mean (standard deviation) | 3557.93 (± 699.19) | 3868.83 (± 3614.89) | 8613.67 (± 3559.69) | 1967.55 (± 1128.69) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: mg/mL | | | | |
| arithmetic mean (standard deviation) | 3501.54 (± 2144.15) | 3161.6 (± 788.14) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Serum Concentration (Tmax)

| | |
|-----------------|--|
| End point title | Time to Reach Maximum Observed Serum Concentration (Tmax) ^[5] |
|-----------------|--|

End point description:

Time to maximum serum concentration (Tmax) of sotatercept, obtained directly from the observed concentration-time data. The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Doses 1-2 predose and postdose at 4 hours, 3, and 7 days after each dose and dose 3 predose.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|-----------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 3 | 3 | 4 |
| Units: days | | | | |

| | | | | |
|-------------------------------|---------------------|------------------------|------------------------|------------------------|
| median (full range (min-max)) | 14.09 (14.01 to 16) | 21.01 (16.16 to 27.98) | 14.02 (13.99 to 16.01) | 18.51 (15.99 to 21.02) |
|-------------------------------|---------------------|------------------------|------------------------|------------------------|

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 2 | | |
| Units: days | | | | |
| median (full range (min-max)) | 0.1688 (0.0035 to 15.99) | 21.06 (20.99 to 21.13) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Estimate of Terminal Elimination Half-Life in Serum at Final Dose Only (t_{1/2})

| | |
|-----------------|---|
| End point title | Estimate of Terminal Elimination Half-Life in Serum at Final Dose Only (t _{1/2}) ^[6] |
|-----------------|---|

End point description:

Terminal elimination half-life (T_{1/2}). The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analyses of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Last dose (Day 99), predose and 4 hours and 3, 7, 14, 21, 28, 56, 84 and 112 days after the final dose.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| | | | | |
|--------------------------------------|--|--|--|---|
| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 4 | 6 | 8 |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 17.6 (± 4.631) | 25.87 (± 7.127) | 21.76 (± 3.941) | 21.03 (± 5.4) |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 4 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 22.46 (± 5.342) | 20.39 (± 5.3) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Lambda (z): Apparent Terminal Rate Constant (at Final Dose Only)

| | |
|-----------------|---|
| End point title | Lambda (z): Apparent Terminal Rate Constant (at Final Dose Only) ^[7] |
|-----------------|---|

End point description:

Lambda, apparent terminal rate constant (final dose only). The PK population included all subjects in the safety population with at least one non-missing plasma concentration data. All analysis of PK data were based on the PK population and subjects were analyzed according to the treatment group to which they were randomized.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Last dose, predose and 4 hours and 3, 7, 14, 21, 28, 56, 84 and 112 days after the final dose.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics (i.e., number of subjects, mean, SD, geometric mean, coefficient of variation (CV%), median, minimum, and maximum) were used to summarize PK parameters for each dose group for PK population. Pharmacokinetic exposure parameters were not estimated for subjects with inadequate PK profiles for 14 days or 28 days or for subjects with dose delays or modifications between Doses 1 and 2.

| | | | | |
|--------------------------------------|---|---|--|---|
| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 4 | 6 | 8 |
| Units: 1/day | | | | |
| arithmetic mean (standard deviation) | 0.0414 (± 0.0094) | 0.0282 (± 0.0071) | 0.0328 (± 0.0063) | 0.0346 (± 0.0078) |

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 4 | | |
| Units: 1/day | | | | |
| arithmetic mean (standard deviation) | 0.0326 (± | 0.0355 (± | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Mean Hemoglobin ≥ 100 g/dL to ≤ 120 g/L Without Rescue Medication

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Mean Hemoglobin ≥ 100 g/dL to ≤ 120 g/L Without Rescue Medication |
|-----------------|---|

End point description:

The percentage of subjects able to maintain a mean hemoglobin concentration ≥ 100 g/dL to ≤ 120 g/L without rescue medication from Visit 14 to Visit 17 (days 99 to 113), defined as the mean of hemoglobin concentrations between Study Day 98 and Study Day 115, inclusive. The Full Analysis Set (FAS) includes all randomized subjects who receive at least one dose of IP.

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

End point timeframe:

Baseline and visit 14 to Visit 17 (days 99 to 113)

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|-------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 7 | 9 | 9 |
| Units: percentage of subjects | | | | |
| number (not applicable) | 42.9 | 42.9 | 11.1 | 33.3 |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 6 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 25 | 50 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Hemoglobin Concentration for Visit 14 to 17 (All Subjects Regardless of Rescue)

| | |
|-----------------|--|
| End point title | Change from Baseline in Mean Hemoglobin Concentration for Visit 14 to 17 (All Subjects Regardless of Rescue) |
|-----------------|--|

End point description:

Baseline hemoglobin value was defined as the mean of three consecutive hemoglobin concentrations with the last hemoglobin concentration measured between the 7th day prior to randomization and the day of randomization, if available. Visit 14 to Visit 17 hemoglobin value was defined as mean of hemoglobin concentrations between Study Day 98 and Study Day 115, inclusive. Includes subjects with non-missing baseline and Day 98 to Day 115 hemoglobin values. Full Analysis Set Population includes all randomized subjects who received at least one dose of Investigational Product.

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

End point timeframe:

Baseline and Visit 14 to Visit 17 (days 99 to 113)

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 5 | 5 | 7 |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | -6.9 (\pm 11.61) | -2.7 (\pm 6.47) | -2.1 (\pm 12.23) | -0.8 (\pm 10.03) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 4 | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | -9.9 (\pm 9.3) | -6.4 (\pm 12.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Hemoglobin Concentration for Visit 14 to 17 (Subjects Not Rescued Prior to Day 115)

| | |
|-----------------|--|
| End point title | Change from Baseline in Mean Hemoglobin Concentration for Visit 14 to 17 (Subjects Not Rescued Prior to Day 115) |
|-----------------|--|

End point description:

Baseline hemoglobin value was defined as the mean of three consecutive hemoglobin concentrations with the last hemoglobin concentration measured between the 7th day prior to randomization and the day of randomization, if available. Visit 14 to Visit 17 hemoglobin value was defined as mean of hemoglobin concentrations between Study Day 98 and Study Day 115, inclusive. Includes subjects with non-missing baseline and Day 98 to Day 115 hemoglobin values. Full Analysis Set Population includes all randomized subjects who received at least one dose of Investigational Product.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Visit 14 to Visit 17 (days 99 to 113) | |

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|--------------------------------------|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 4 | 2 | 6 |
| Units: g/L) | | | | |
| arithmetic mean (standard deviation) | -7 (± 6.24) | -3.6 (± 7.08) | -0.3 (± 15.2) | 0.5 (± 10.28) |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 3 | | |
| Units: g/L) | | | | |
| arithmetic mean (standard deviation) | -13 (± 10.07) | -1 (± 8.05) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

| | |
|-----------------|--|
| End point title | Number of Participants With Adverse Events (AEs) |
|-----------------|--|

End point description:

Treatment-emergent adverse event (TEAE) was defined as an adverse event with start date on or after date of first dose of study drug. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. A serious adverse event is defined as any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. Severity and intensity was assessed using the following grading scale: Mild, Moderate and Severe (could be non-serious or serious).

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

End point timeframe:

From date of first dose of investigational product to 112 days after the last dose of investigational product or until the last study visit, whichever period was longer. The maximum duration for any IV or SC dose was 114 days.

| End point values | Group 1: Sotatercept 0.1 mg/kg Intravenous (IV) injection | Group 1: Sotatercept 0.13 mg/kg Subcutaneous (SC) injection | Group 2: Sotatercept 0.2 mg/kg IV injection | Group 2: Sotatercept 0.26 mg/kg SC injection |
|---|---|---|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 7 | 9 | 9 |
| Units: subjects | | | | |
| Any TEAE | 7 | 3 | 9 | 6 |
| Any treatment related TEAE | 1 | 1 | 1 | 0 |
| Any serious TEAE | 3 | 0 | 3 | 1 |
| Any treatment-related serious TEAE | 0 | 0 | 0 | 0 |
| Any TEAE leading to study drug discontinuation | 0 | 0 | 3 | 0 |
| Any severe TEAE | 0 | 0 | 2 | 0 |
| Any TEAE leading to death | 0 | 0 | 0 | 0 |

| End point values | Group 3: Sotatercept 0.1 – 0.4 mg/kg IV injection | Group 3: Sotatercept 0.4 – 0.5 mg/kg SC injection | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 6 | | |
| Units: subjects | | | | |
| Any TEAE | 10 | 6 | | |
| Any treatment related TEAE | 0 | 1 | | |
| Any serious TEAE | 3 | 3 | | |
| Any treatment-related serious TEAE | 0 | 0 | | |
| Any TEAE leading to study drug discontinuation | 1 | 0 | | |
| Any severe TEAE | 1 | 2 | | |
| Any TEAE leading to death | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of IP up to final/early termination visit or 112 +/- 3 days after the last dose of sotatercept. The maximum duration of exposure to IP for any IV/SC dose was 114 days.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Sotatercept 0.1 mg/kg IV |
|-----------------------|--------------------------|

Reporting group description:

Subjects received sotatercept at 0.1 mg/kg administered IV every 14 days for up to 8 doses to evaluate the Pharmacokinetic (PK) and safety of IV versus subcutaneous (SC) dosing of sotatercept.

| | |
|-----------------------|---------------------------|
| Reporting group title | Sotatercept 0.13 mg/kg SC |
|-----------------------|---------------------------|

Reporting group description:

Subjects received sotatercept at 0.13 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|-----------------------|--------------------------|
| Reporting group title | Sotatercept 0.2 mg/kg IV |
|-----------------------|--------------------------|

Reporting group description:

Subjects received sotatercept at 0.2 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|-----------------------|---------------------------|
| Reporting group title | Sotatercept 0.26 mg/kg SC |
|-----------------------|---------------------------|

Reporting group description:

Subjects received sotatercept at 0.26 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Sotatercept 0.1 to 0.4 mg/kg IV |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received sotatercept at a starting dose of 0.1 mg/kg that could be increased up to a dose of 0.4 mg/kg administered IV every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Sotatercept 0.4 to 0.5 mg/kg SC |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received sotatercept at 0.4 mg/kg that could be increased up to a dose of 0.5 mg/kg administered SC every 14 days for up to 8 doses to evaluate the PK and safety of IV versus SC dosing of sotatercept.

| Serious adverse events | Sotatercept 0.1 mg/kg IV | Sotatercept 0.13 mg/kg SC | Sotatercept 0.2 mg/kg IV |
|---|--------------------------|---------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | 0 / 7 (0.00%) | 3 / 9 (33.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous graft site stenosis | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shunt thrombosis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access malfunction | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal angiodysplasia haemorrhagic | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Sotatercept 0.26 mg/kg SC | Sotatercept 0.1 to 0.4 mg/kg IV | Sotatercept 0.4 to 0.5 mg/kg SC |
|---|---------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 3 / 12 (25.00%) | 3 / 6 (50.00%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous graft site stenosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shunt thrombosis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular access malfunction | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiopulmonary failure | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal angiodysplasia haemorrhagic | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Sotatercept 0.1 mg/kg IV | Sotatercept 0.13 mg/kg SC | Sotatercept 0.2 mg/kg IV |
|---|--------------------------|---------------------------|--------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 7 (100.00%) | 3 / 7 (42.86%) | 9 / 9 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Juvenile melanoma benign subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Vascular disorders | | | |
| Extravasation blood subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Extremity necrosis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Haematoma subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Hypertension subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 2 / 9 (22.22%) 2 |
| Hypotension subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 1 / 7 (14.29%) 3 | 1 / 9 (11.11%) 3 |
| Pallor subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Catheter site pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Face oedema subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Oedema peripheral | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 4 | 1 / 7 (14.29%) 1 | 1 / 9 (11.11%) 1 |
| Reproductive system and breast disorders Postmenopausal haemorrhage subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 2 / 9 (22.22%) 2 |
| Nasal obstruction subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Pulmonary hypertension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Respiratory acidosis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Investigations | | | |

| | | | |
|---|---------------------|---------------------|--------------------|
| Cardioactive drug level increased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula site complication subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 2 / 7 (28.57%) 3 | 0 / 9 (0.00%) 0 |
| Arteriovenous fistula site haematoma subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 |
| Arteriovenous fistula site haemorrhage subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Foreign body subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Haemodialysis-induced symptom subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 |
| Hand fracture subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Post-traumatic pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Procedural hypotension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 |
| Wound secretion | | | |

| | | | |
|---|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Cardiac disorders | | | |
| Angina pectoris subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 2 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Nervous system disorders | | | |
| Diabetic neuropathy subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Ischaemic stroke subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Pancytopenia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Eye disorders | | | |
| Amaurosis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Amaurosis fugax subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Choroidal effusion | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 7 (14.29%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|--|---|---|
| Vomiting subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Pruritus generalised subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Renal colic subjects affected / exposed occurrences (all) Renal cyst subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 4 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 |
| Endocrine disorders Hyperparathyroidism subjects affected / exposed occurrences (all) Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain | 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Tendonitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 7 (14.29%) 1 | 1 / 9 (11.11%) 1 |
| Localised infection subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 0 / 7 (0.00%) 0 | 1 / 9 (11.11%) 2 |
| Metabolism and nutrition disorders | | | |
| Calciophylaxis subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Folate deficiency | | | |

| | | | |
|-----------------------------|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 7 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Sotatercept 0.26 mg/kg SC | Sotatercept 0.1 to 0.4 mg/kg IV | Sotatercept 0.4 to 0.5 mg/kg SC |
|---|---------------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 9 (66.67%) | 9 / 12 (75.00%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Juvenile melanoma benign | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Extravasation blood | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 2 / 12 (16.67%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 2 | 2 |
| Hypotension | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Pallor subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Catheter site pain subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Face oedema subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 6 (16.67%) 2 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Nasal obstruction subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Pulmonary hypertension subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Respiratory acidosis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Investigations Cardioactive drug level increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Injury, poisoning and procedural complications Arteriovenous fistula site complication subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 3 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Arteriovenous fistula site haematoma subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Arteriovenous fistula site haemorrhage subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Fall | | | |

| | | | |
|-------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemodialysis-induced symptom | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Procedural hypotension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 2 | 3 / 6 (50.00%) 3 |
| Ischaemic stroke subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Blood and lymphatic system disorders Pancytopenia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Eye disorders Amaurosis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Amaurosis fugax subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Choroidal effusion subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Chronic gastritis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Diarrhoea | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Intra-abdominal haematoma | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 5 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal colic | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Renal cyst subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Endocrine disorders Hyperparathyroidism subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 3 | 0 / 12 (0.00%) 0 | 2 / 6 (33.33%) 6 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 0 / 12 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Tendonitis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 6 (0.00%) 0 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 6 (16.67%) 1 |
| Cellulitis | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Calciphylaxis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Folate deficiency | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 12 (8.33%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 12 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 05 September 2013 | <p>1. Changed Part 1 interim analysis trigger to occur after the 6th subject, instead of 3rd subject, had 14 days follow up after the 3rd IV or SQ dose in each arm. 2. Removed the dose group discontinuation rule for inadequate Hgb response (defined as Hgb concentration < 9.5 g/dL or a > 1 g/L decrease from baseline, 14 days after the 3rd IV or SQ dose in 2 of 3 subjects in either arm). 3. Added new predefined safety criteria for closure of an IV or SQ arm to further enrollment, with discontinuation of sotatercept in each arm if the following were met in 4 of 6 subjects in each arm, prior to receiving rescue therapy: • Hgb discontinuation rule for re-dosing • BP discontinuation rule for re-dosing • SAE considered related to sotatercept 4. Modification to include a threshold BP rule for discontinuation of IP if the pre or postdose mean home systolic BP was > 200 mm Hg or the mean pre or postdose home diastolic BP was > 110 mm Hg at any time during the study. 5. Clarification was provided for reassessment of the mean predose home BP measurements if the BP stopping rule was achieved (but not above the threshold BP [systolic BP > 200 mm Hg and diastolic BP > 100 mm Hg]). 6. The postdose home BP assessment was extended to a 2-day interval, with a minimum of 1 set of 3 measurements after waking and 1 set of 3 measurements before bed required for an adequate sample. 7. Clarification on the identification of AEs of special interest for discontinuation by relating it to the Reference Safety Information in the Sotatercept Investigator's Brochure which includes increases in Hgb, hematocrit, red blood cells and BP. 8. Information summarizing the frequency of hypersensitivity reactions in the product labels of several Fc fusion protein therapeutics and rituximab; recommendations for handling of hypersensitivity reactions from these labels was also added 9. Free testosterone and estradiol and uncertainties concerning the IPs action on fertility were added to the protocol</p> |
| 17 December 2014 | <p>1. The study design for Part 1, Dose Group 3 was modified to an intrasubject dose escalation design to accommodate an apparent change in Hb response over time, due to an underlying ESA effect washout. Intrasubject dose escalation was implemented in response to subjects' individual Hb levels both in the IV and SC arms. 2. Dose escalation in Part 1, Dose Group 3 was allowed in increments of 0.1 mg/kg until reaching 0.4 mg/kg every 14 days for the IV arm and 0.5 mg/kg every 14 days for the SC arm. 3. New dose escalation rules were added for both the IV and SQ arms and one of the dose-holding rules was modified to include an absolute Hb level of > 11 g/dL (> 110 g/L) in addition to the increase in Hb of ≥ 1 g/dL (≥ 10 g/L). 4. Sample size was increased to 12 to 18 subjects in the IV arm of Part 1, Dose Group 3 and the randomization was accordingly changed to 2:1, IV versus SC. 5. The ESA-free phase was increased to 10 days for subjects who were on darbepoetin administered by SQ route before entering the study. 6. A mandatory testing for Hb levels by central laboratory method was required for the 3 values of predialysis Hb concentrations for calculation of mean Hb concentration during the screening period. In addition, the predialysis Hb value for dosing eligibility was required by both central laboratory and local methods. 7. A clarification was added for long-term evaluation of anti-sotatercept antibodies based on the last available anti-sotatercept antibody positive result at the time of Final/Early Termination Visit, instead of the sample collected at the Final/Early Termination Visit.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to a shift in the clinical development strategy for the renal sotatercept program, Part 2 of the study was not conducted; Part 2 objectives were not assessed and none of the statistical analyses in Part 2 were conducted; no safety concerns.

Notes: