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	255.8	250.7	259
standard deviation	± 25.67	± 18.09	± 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 (Cmax28d) Obtained From the Combined First 2 Doses

End point title	Maximum Observed Serum Concentration (Cmax28d) Obtained From the Combined First 2 Doses[4]

End point description:

Maximum observed serum concentration (Cmax28d) 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 (t1/2)

End point title	Estimate of Terminal Elimination Half-Life in Serum at Final Dose Only (t1/2)[6]

End point description:

Terminal elimination half-life (T1/2). 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 (±		

0.0085)	0.0077)

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 (± 11.61)	-2.7 (± 6.47)	-2.1 (± 12.23)	-0.8 (± 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 (± 9.3)	-6.4 (± 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	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Extravasation blood			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Extremity necrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	2	3	3
Pallor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			

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

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

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Ischaemic stroke			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Amaurosis fugax			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	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	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	4	0	1
Renal colic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Localised infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	2
Metabolism and nutrition disorders			
Calciphylaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	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	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pallor			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Nasal obstruction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pulmonary hypertension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory acidosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Investigations			
Cardioactive drug level increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	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	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	3 / 6 (50.00%)
occurrences (all)	0	2	3
Ischaemic stroke			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Amaurosis fugax			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Choroidal effusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chronic gastritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	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	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	3 / 9 (33.33%)	0 / 12 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	6
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Tendonitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	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	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
17 December 2014	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.

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: