



Clinical trial results:

AN OPEN-LABEL, RANDOMIZED, PHASE 2, PARALLEL, DOSE-RANGING, MULTICENTER STUDY OF SOTATERCEPT FOR THE TREATMENT OF PATIENTS WITH ANEMIA AND LOW- OR INTERMEDIATE-1 RISK MYELOYDYSPLASTIC SYNDROMES OR NON-PROLIFERATIVE CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

Summary

EudraCT number	2012-002601-22
Trial protocol	FR
Global end of trial date	29 April 2018

Results information

Result version number	v1 (current)
This version publication date	16 May 2019
First version publication date	16 May 2019

Trial information

Trial identification

Sponsor protocol code	ACE-011-MDS-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01736683
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, New Jersey, United States, 07901
Public contact	ClinicalTrialDisclosure, Celgene Corporation, +1 888260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	ClinicalTrialDisclosure, Celgene Corporation, +1 888260-1599, ClinicalTrialDisclosure@celgene.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine a safe, tolerable and effective dose of sotatercept that results in the greatest frequency of improvement of anemia in patients diagnosed with low- or intermediate-1 risk MDS or non-proliferative chronic myelomonocytic leukemia (CMML).

Protection of trial subjects:

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that Celgene, its authorized representative, and investigator abided by Good Clinical Practice (GCP), as described in the International Council for Harmonisation (ICH) E6 guideline and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study received approval from an independent review board/ ethics committee (IRB/IEC) prior to commencement. The investigator conducted all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities. An informed consent form (ICF) explaining the procedures of the study, including the potential hazards, was reviewed and approved by the IRB/IEC prior to its use. The investigator obtained informed consent of a subject and/or a subject's legal representative prior to any study-related procedures. Documentation, including the date, that informed consent occurred prior to the subject's entry into the study, and of the informed consent process was recorded in the subject's source documents. The original ICF, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, was maintained in the investigator's study files and a copy was given to the subject. In addition, the ICF was revised when the protocol was amended in a way that impacted the content of the informed consent. Subjects participating in the study when the amended protocol was implemented were reconsented with the revised version of the ICF. The revised ICF, signed and dated by the subject and by the person consenting the subject, was maintained in the investigator's study files, and a copy was given to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	74
EEA total number of subjects	24

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)	17
From 65 to 84 years	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were stratified by concentration of serum erythropoietin (EPO) (<500 versus ≥500 IU/L), by number of transfusions within 56 days of study enrollment (<4 versus ≥4 units of red blood cells) and assigned randomly to 0.1 mg/kg and 0.3 mg/kg arms.

Pre-assignment

Screening details:

Enrollment in the other arms (sotatercept 0.5, 1.0 and 2.0 mg/kg arms) commenced after the Steering Committee approved the higher doses based on the safety of preceding doses.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sotatercept 0.1 mg/kg

Arm description:

Sotatercept 0.1 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in ≤ 1/5 subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.

Arm type	Experimental
Investigational medicinal product name	Sotatercept
Investigational medicinal product code	
Other name	ACE-011, ActRIIA-IgG1Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sotatercept is supplied as a lyophilized powder that is reconstituted using Water for Injection (WFI) and administered as a subcutaneous (SC) injection by the study staff at the clinical site.

Arm title	Sotatercept 0.3 mg/kg
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Arm description:

Sotatercept 0.3 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in ≤ 1/5 subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.

Arm type	Experimental
Investigational medicinal product name	Sotatercept
Investigational medicinal product code	
Other name	ACE-011, ActRIIA-IgG1Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sotatercept is supplied as a lyophilized powder that is reconstituted using Water for Injection (WFI) and administered as a subcutaneous (SC) injection by the study staff at the clinical site.

Arm title	Sotatercept 0.5 mg/kg
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Arm description:

Sotatercept 0.5 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 0.5 mg/kg treatment group, the 1.0 mg/kg treatment group began inclusion in the randomization scheme.

Arm type	Experimental
Investigational medicinal product name	Sotatercept
Investigational medicinal product code	
Other name	ACE-011, ActRIIA-IgG1Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sotatercept is supplied as a lyophilized powder that is reconstituted using Water for Injection (WFI) and administered as a subcutaneous (SC) injection by the study staff at the clinical site.

Arm title	Sotatercept 1.0 mg/kg
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Arm description:

Sotatercept 1.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 1.0 mg/kg treatment group, the 2.0 mg/kg treatment group began inclusion in the randomization scheme. Following evaluation of all treatment group data by the Steering Committee, enrollment continued only in the 1.0 mg/kg arm because the arm had the greatest frequency of erythroid hematological improvement (HI-E).

Arm type	Experimental
Investigational medicinal product name	Sotatercept
Investigational medicinal product code	
Other name	ACE-011, ActRIIA-IgG1Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sotatercept is supplied as a lyophilized powder that is reconstituted using Water for Injection (WFI) and administered as a subcutaneous (SC) injection by the study staff at the clinical site.

Arm title	Sotatercept 2.0 mg/kg
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Arm description:

Sotatercept 2.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled participants by protocol amendment.

Arm type	Experimental
Investigational medicinal product name	Sotatercept
Investigational medicinal product code	
Other name	ACE-011, ActRIIA-IgG1Fc
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Sotatercept is supplied as a lyophilized powder that is reconstituted using Water for Injection (WFI) and administered as a subcutaneous (SC) injection by the study staff at the clinical site.

Number of subjects in period 1	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Started	7	6	21
Completed	0	0	0
Not completed	7	6	21
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	3
Adverse event, non-fatal	-	1	2
Disease relapse	-	-	2
Lack of therapeutic effect	7	4	13
Progressive disease	-	-	-
not specified	-	-	1

Number of subjects in period 1	Sotatercept 1.0 mg/kg	Sotatercept 2.0 mg/kg
Started	35	5
Completed	0	0
Not completed	35	5
Adverse event, serious fatal	-	-
Consent withdrawn by subject	1	1
Adverse event, non-fatal	3	2
Disease relapse	1	-
Lack of therapeutic effect	20	1
Progressive disease	1	-
not specified	9	1

Baseline characteristics

Reporting groups

Reporting group title	Sotatercept 0.1 mg/kg
Reporting group description: Sotatercept 0.1 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 0.3 mg/kg
Reporting group description: Sotatercept 0.3 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 0.5 mg/kg
Reporting group description: Sotatercept 0.5 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 0.5 mg/kg treatment group, the 1.0 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 1.0 mg/kg
Reporting group description: Sotatercept 1.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 1.0 mg/kg treatment group, the 2.0 mg/kg treatment group began inclusion in the randomization scheme. Following evaluation of all treatment group data by the Steering Committee, enrollment continued only in the 1.0 mg/kg arm because the arm had the greatest frequency of erythroid hematological improvement (HI-E).	
Reporting group title	Sotatercept 2.0 mg/kg
Reporting group description: Sotatercept 2.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled participants by protocol amendment.	

Reporting group values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Number of subjects	7	6	21
Age categorical Units: Subjects			
<65 years	3	0	7
>=65 to <75 years	2	3	8
>=75 years	2	3	6
Age continuous Units: years			
arithmetic mean	67	75	69
standard deviation	± 8.3	± 6.9	± 8.0
Gender categorical Units: Subjects			
Female	3	0	4

Male	4	6	17
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Red Blood Cell (RBC) Transfusion Burden Categories			
RBC units transfused during 56 days prior to the start of treatment.			
Units: Subjects			
<4 units (Low Transfusion Burden)	0	0	3
>=4 units (High Transfusion Burden)	7	6	18
Number of Previous Erythropoiesis-Stimulating Agents (ESA) Therapies for Myelodysplastic Syndromes			
Units: Subjects			
0 ESA therapies	1	0	1
1 ESA therapy	6	2	11
2 ESA therapies	0	4	8
3 ESA therapies	0	0	1
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	6	14
Unknown or Not Reported	0	0	6
Other	0	0	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	7	6	13
Missing	0	0	6
Erythropoietin Level			
Units: Subjects			
<=200 mIU/mL	2	3	6
>200 to <=500 mIU/mL	2	1	6
>500 mIU/mL	3	2	9
Missing	0	0	0
Number of Previous Non-ESA Agents for Myelodysplastic Syndromes			
Units: Subjects			
0 non-ESA agents	0	0	2
1 non-ESA agent	1	0	7
2 non-ESA agents	2	1	6
3 non-ESA agents	2	1	2
4 non-ESA agents	0	1	2
5 non-ESA agents	1	1	0
>5 non-ESA agents	1	2	2
International Prognostic Scoring System (IPSS)			
The International Prognostic Scoring System for MDS (IPSS) assigns a prognostic score (0=good and increasing in risk by half-grades with the top score outlined below) for three prognostic variables: • Marrow blasts (score 0-2.0 • Karyotype (score 0-1.0) • Cytopenias: neutrophil, platelets, and Hg counts			

(score 0-0.5) The three individual scores are summed resulting in a full range of 0- 3.5 and placed into risk categories • 0 = low risk • 0.5-1.0 = intermediate-1 risk • 1.5-2.0 = intermediate-2 risk • ≥ 2.5 = high risk

Units: Subjects			
Low - 0	4	4	5
Intermediate-1: 0.5 to 1.0	3	2	16
Intermediate-2: 1.5 to 2	0	0	0
High: ≥ 2.5	0	0	0
Height			
Units: cm			
arithmetic mean	1.70	1.75	1.70
standard deviation	± 0.110	± 0.054	± 0.093
Weight			
Units: kg			
arithmetic mean	85.3	79.5	77.9
standard deviation	± 21.79	± 13.90	± 13.97

Reporting group values	Sotatercept 1.0 mg/kg	Sotatercept 2.0 mg/kg	Total
Number of subjects	35	5	74
Age categorical			
Units: Subjects			
<65 years	6	1	17
≥ 65 to <75 years	17	2	32
≥ 75 years	12	2	25
Age continuous			
Units: years			
arithmetic mean	71	69	-
standard deviation	± 8.2	± 13.0	-
Gender categorical			
Units: Subjects			
Female	17	4	28
Male	18	1	46
Red Blood Cell (RBC) Transfusion Burden Categories			
RBC units transfused during 56 days prior to the start of treatment.			
Units: Subjects			
<4 units (Low Transfusion Burden)	8	1	12
≥ 4 units (High Transfusion Burden)	27	4	62
Number of Previous Erythropoiesis- Stimulating Agents (ESA) Therapies for Myelodysplastic Syndromes			
Units: Subjects			
0 ESA therapies	0	0	2
1 ESA therapy	23	3	45
2 ESA therapies	10	2	24
3 ESA therapies	2	0	3
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	1	0	1
White	18	3	48
Unknown or Not Reported	16	1	23
Other	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	19	4	49
Missing	16	1	23
Erythropoietin Level Units: Subjects			
<=200 mIU/mL	16	2	29
>200 to <=500 mIU/mL	6	0	15
>500 mIU/mL	9	2	25
Missing	4	1	5
Number of Previous Non-ESA Agents for Myelodysplastic Syndromes Units: Subjects			
0 non-ESA agents	7	2	11
1 non-ESA agent	16	1	25
2 non-ESA agents	7	1	17
3 non-ESA agents	2	1	8
4 non-ESA agents	3	0	6
5 non-ESA agents	0	0	2
>5 non-ESA agents	0	0	5
International Prognostic Scoring System (IPSS)			
The International Prognostic Scoring System for MDS (IPSS) assigns a prognostic score (0=good and increasing in risk by half-grades with the top score outlined below) for three prognostic variables: • Marrow blasts (score 0-2.0 • Karyotype (score 0-1.0) • Cytopenias: neutrophil, platelets, and Hg counts (score 0-0.5) The three individual scores are summed resulting in a full range of 0- 3.5 and placed into risk categories • 0 = low risk • 0.5-1.0 = intermediate-1 risk • 1.5-2.0 = intermediate-2 risk • >=2.5 = high risk			
Units: Subjects			
Low - 0	11	0	24
Intermediate-1: 0.5 to 1.0	24	5	50
Intermediate-2: 1.5 to 2	0	0	0
High: >=2.5	0	0	0
Height Units: cm			
arithmetic mean	1.68	1.56	
standard deviation	± 0.089	± 0.043	-
Weight Units: kg			
arithmetic mean	73.5	56.4	
standard deviation	± 15.55	± 7.25	-

End points

End points reporting groups

Reporting group title	Sotatercept 0.1 mg/kg
Reporting group description: Sotatercept 0.1 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 0.3 mg/kg
Reporting group description: Sotatercept 0.3 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 0.5 mg/kg
Reporting group description: Sotatercept 0.5 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 0.5 mg/kg treatment group, the 1.0 mg/kg treatment group began inclusion in the randomization scheme.	
Reporting group title	Sotatercept 1.0 mg/kg
Reporting group description: Sotatercept 1.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 1.0 mg/kg treatment group, the 2.0 mg/kg treatment group began inclusion in the randomization scheme. Following evaluation of all treatment group data by the Steering Committee, enrollment continued only in the 1.0 mg/kg arm because the arm had the greatest frequency of erythroid hematological improvement (HI-E).	
Reporting group title	Sotatercept 2.0 mg/kg
Reporting group description: Sotatercept 2.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled participants by protocol amendment.	

Primary: Percentage of Participants With Erythroid Hematological Improvement (HI-E) Starting Before the Completion of Five Cycles of Treatment (Responder Rate)

End point title	Percentage of Participants With Erythroid Hematological Improvement (HI-E) Starting Before the Completion of Five Cycles of Treatment (Responder Rate) ^[1]
End point description: Responder rate includes non-transfusion dependent efficacy (NTDE) participants and transfusion dependent efficacy (TDE) participants. For nontransfusion dependence efficacy (NTDE) participants who required < 4 units of RBCs in the 8 weeks prior to start of therapy, HI-E was defined as an increase of ≥ 1.5 g/dL hemoglobin sustained for 56 days over a period of ≥ 8 weeks. For transfusion dependence efficacy (TDE) participants who required ≥ 4 units of RBCs in the 8 weeks prior to start of therapy, HI-E was defined as a decrease of ≥ 4 units of RBCs transfused sustained for 56 days over a period of 8 weeks.	
End point type	Primary
End point timeframe: Day 2 - 142	

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: There were no statistical analysis performed.

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[2]	6 ^[3]	21 ^[4]	35 ^[5]
Units: percentage of participants				
number (not applicable)				
All participants	0	66.7	42.9	60.0
NTDE subpopulation	0	0	33.3	62.5
TDE subpopulation	0	66.7	44.4	59.3

Notes:

[2] - All - 7 participants NTDE - 0 participants TDE - 7 participants

[3] - All - 6 participants NTDE - 0 participants TDE - 6 participants

[4] - All - 21 participants NTDE - 3 participants TDE - 18 participants

[5] - All - 35 participants NTDE - 8 participants TDE - 27 participants

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[6]			
Units: percentage of participants				
number (not applicable)				
All participants	40.0			
NTDE subpopulation	100			
TDE subpopulation	25.0			

Notes:

[6] - All - 5 participants NTDE - 1 participant TDE - 4 participants

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Limiting Toxicities (DLTs)

End point title	Dose Limiting Toxicities (DLTs)
End point description:	
The following were DLTs if the investigator suspected they were treatment related: 1. Increase to ≥ 140 mmHg systolic blood pressure 2. Increase to ≥ 90 mmHg diastolic blood pressure 3. Increase to ≥ 140 systolic and increase > 20 mmHg compared to baseline systolic 4. Increase to ≥ 90 mmHg diastolic and increase > 20 mmHg compared to baseline diastolic. 5. Introduction of new anti-hypertension medication during treatment 6. Increase in dose of baseline anti-hypertension medication during treatment 7. \geq Grade 2 (moderate severity or worse) hypertension as an adverse event	
End point type	Secondary
End point timeframe:	
Day 1 to 59.2 months	

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	21	35
Units: participants				
1. Increase to ≥ 140 mmHg systolic	1	1	8	19
2. Increase to ≥ 90 mmHg diastolic	0	0	2	2
3. ≥ 140 systolic and increase > 20 mmHg base	0	1	5	10
4. ≥ 90 mmHg diastolic and increase > 20 mmHg base	0	0	2	2
5. Introduction of new anti-hypertension med	0	0	4	3
6. $>$ in dose of baseline anti-hypertension med	0	0	0	0
7. \geq Grade 2 hypertension TEAE	0	1	2	4

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: participants				
1. Increase to ≥ 140 mmHg systolic	2			
2. Increase to ≥ 90 mmHg diastolic	1			
3. ≥ 140 systolic and increase > 20 mmHg base	2			
4. ≥ 90 mmHg diastolic and increase > 20 mmHg base	1			
5. Introduction of new anti-hypertension med	1			
6. $>$ in dose of baseline anti-hypertension med	0			
7. \geq Grade 2 hypertension TEAE	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Erythroid Hematological Improvement (HI-E) Response

End point title	Time to Erythroid Hematological Improvement (HI-E) Response
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End point description:

Time to first response = start date of first response (HI-E) - first dose date + 1 day. For NTDE participants (who required < 4 units of RBCs in the 8 weeks prior to start of therapy), HI-E was defined as an increase of ≥ 1.5 g/dL hemoglobin sustained for 56 days over a period of ≥ 8 weeks. For TDE participants (who required ≥ 4 units of RBCs in the 8 weeks prior to start of therapy), HI-E was defined as a decrease of ≥ 4 units of RBCs transfused sustained for 56 days over a period of 8 weeks. 9999 = not applicable

End point type	Secondary
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End point timeframe:

Day 1 to Day 87

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[7]	4 ^[8]	9 ^[9]	21 ^[10]
Units: days				
median (full range (min-max))				
All participants	(to)	24.0 (2 to 44)	1.0 (1 to 2)	1.0 (1 to 86)
NTDE subpopulation	(to)	9999 (9999 to 9999)	1.0 (1 to 1)	1.0 (1 to 52)
TDE subpopulation	(to)	24.0 (2 to 44)	1.5 (1 to 2)	1.5 (1 to 86)

Notes:

[7] - Participants who responded

[8] - Participants who responded Total = 4 NTDE = 0 TDE = 4

[9] - Participants who responded Total = 9 NTDE = 1 TDE = 8

[10] - Participants who responded Total = 21 NTDE = 5 TDE = 16

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[11]			
Units: days				
median (full range (min-max))				
All participants	48.0 (9 to 87)			
NTDE subpopulation	9.0 (9 to 9)			
TDE subpopulation	87 (87 to 87)			

Notes:

[11] - Participants who responded Total = 2 NTDE = 1 TDE = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Erythroid Hematological Improvement (HI-E)

End point title	Duration of Erythroid Hematological Improvement (HI-E)
End point description:	
The duration of HI-E response for participants who responded was (the last date of the consecutive hemoglobin [Hgb] measurements of the first ≥ 56 day interval) – (the first date of the consecutive Hgb measurements of the first ≥ 56 day interval) + 1 day. 9999 = not applicable	
End point type	Secondary
End point timeframe:	
Day 1 to 183.7 weeks	

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[12]	4 ^[13]	9 ^[14]	21 ^[15]
Units: days				
median (full range (min-max))				
All participants	(to)	62.5 (62 to 69)	104.0 (56 to 1794)	133.0 (58 to 1554)
NTDE subpopulation	(to)	9999 (9999 to 9999)	79.0 (79 to 79)	1043.0 (69 to 1554)
TDE subpopulation	(to)	62.5 (62 to 69)	105.5 (56 to 1794)	96.5 (58 to 1033)

Notes:

[12] - Efficacy Evaluable Population of participants who responded

[13] - Efficacy Evaluable Population of participants who responded Total = 4 NTDE = 0 TDE = 4

[14] - Efficacy Evaluable Population of participants who responded Total = 9 NTDE = 1 TDE = 8

[15] - Efficacy Evaluable Population of participants who responded Total = 21 NTDE = 5 TDE = 16

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[16]			
Units: days				
median (full range (min-max))				
All participants	96.0 (58 to 134)			
NTDE subpopulation	134.0 (134 to 134)			
TDE subpopulation	58.0 (58 to 58)			

Notes:

[16] - Efficacy Evaluable Population of participants who responded Total = 2 NTDE = 1 TDE = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression to Acute Myeloid Leukemia (AML) for Participants Who Had Progression

End point title	Time to Progression to Acute Myeloid Leukemia (AML) for Participants Who Had Progression
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End point description:

Progression to AML used criteria by the International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006). Progression is considered if any of the following are met: • $\geq 50\%$ increase in blasts • $\geq 50\%$ decrement from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 2 g/dL • Transfusion dependence This outcome was defined as a Kaplan-Meier estimate however few participants progressed so a Kaplan-Meier analysis could not be performed. Disclosed are time to progression values only for participants who did progress to AML.

End point type	Secondary
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End point timeframe:

Day 1 to 183.7 weeks

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[17]	0 ^[18]	1 ^[19]	1 ^[20]
Units: weeks				
number (not applicable)			45.6	78.0

Notes:

[17] - Efficacy Evaluable Population of participants who progressed to AML

[18] - Efficacy Evaluable Population of participants who progressed to AML

[19] - Efficacy Evaluable Population of participants who progressed to AML

[20] - Efficacy Evaluable Population of participants who progressed to AML

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[21]			
Units: weeks				
number (not applicable)				

Notes:

[21] - Efficacy Evaluable Population of participants who progressed to AML

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression to Events of Higher Risk Myelodysplastic Syndromes (MDS) Using the International Prognostic Scoring System (IPSS) For Participants Who Had Progression

End point title	Time to Progression to Events of Higher Risk Myelodysplastic Syndromes (MDS) Using the International Prognostic Scoring System (IPSS) For Participants Who Had Progression
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End point description:

Progression to events of higher risk MDS used criteria from the International Prognostic Scoring System for MDS (IPSS) which assigns a prognostic score (0=good and increasing in risk by half-grades with the top score outlined below) for three prognostic variables: • Marrow blasts (score 0-2.0) • Karyotype (score 0-1.0) • Cytopenias: neutrophil, platelets, and Hg counts (score 0-0.5) The three individual scores are summed resulting in a full range of 0- 3.5 and placed into risk categories • 0 = low risk • 0.5-1.0 = intermediate-1 risk • 1.5-2.0 =intermediate-2 risk • >=2.5 = high risk This outcome was defined as a Kaplan-Meier estimate however few participants progressed so a Kaplan-Meier analysis could not be performed. Data reported represent event times (weeks) for participants who did progress to higher risk MDS categories.

End point type	Secondary
End point timeframe:	
Day 1 to 257.3 weeks	

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1 ^[22]	0 ^[23]	1 ^[24]	1 ^[25]
Units: weeks				
number (not applicable)	15.1		24.7	67.4

Notes:

[22] - Efficacy Evaluable Population of participants who progressed to high risk MDS categories

[23] - Efficacy Evaluable Population of participants who progressed to high risk MDS categories

[24] - Efficacy Evaluable Population of participants who progressed to high risk MDS categories

[25] - Efficacy Evaluable Population of participants who progressed to high risk MDS categories

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[26]			
Units: weeks				
number (not applicable)				

Notes:

[26] - Efficacy Evaluable Population of participants who progressed to high risk MDS categories

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Progression-free Survival

End point title	Kaplan-Meier Estimates for Progression-free Survival
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End point description:

Participants who had disease progression were considered to have events. Participants who died without acute myeloid leukemia (AML) were also considered to have events with the event date as the date of death. Those who did not have disease progression and who were lost to follow-up were censored at the last known disease progression assessment date. Participants without disease progression at the last follow-up contact were censored at the date of the last followup contact date. Disease Progression to AML used criteria by the International Working Group (IWG) Response Criteria in Myelodysplasia (Cheson, 2006). Progression is considered if any of the following are met: • $\geq 50\%$ increase in blasts • $\geq 50\%$ decrement from maximum remission/response levels in granulocytes or platelets • Reduction in hemoglobin (Hgb) concentration by ≥ 2 g/dL • Transfusion dependence 9999 = not enough events to allow for calculation

End point type	Secondary
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End point timeframe:

Day 1 to 257.3 weeks

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[27]	6 ^[28]	21 ^[29]	35 ^[30]
Units: weeks				
median (confidence interval 95%)	82.7 (15.1 to 82.7)	9999 (91.1 to 9999)	9999 (58.6 to 9999)	9999 (9999 to 9999)

Notes:

[27] - Efficacy Evaluable Population

[28] - Efficacy Evaluable Population

[29] - Efficacy Evaluable Population

[30] - Efficacy Evaluable Population

End point values	Sotatercept 2.0 mg/kg			
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Subject group type	Reporting group			
Number of subjects analysed	5 ^[31]			
Units: weeks				
median (confidence interval 95%)	9999 (79.9 to 9999)			

Notes:

[31] - Efficacy Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Overall Survival (OS)

End point title	Kaplan-Meier Estimates for Overall Survival (OS)
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End point description:

OS was defined as the time between start of treatment and the death/censored date. Participants who died (regardless of the cause of death) were considered to have an event. Participants who were alive at the end of the study, and participants who were lost to follow-up, were censored at the last date when subjects were known to be alive. 9999 = not enough events to allow for calculation

End point type	Secondary
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End point timeframe:

Day 1 to 257.3 weeks

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[32]	6 ^[33]	21 ^[34]	35 ^[35]
Units: weeks				
median (confidence interval 95%)	82.7 (-9999 to 9999)	9999 (91.0 to 9999)	9999 (58.6 to 9999)	9999 (9999 to 9999)

Notes:

[32] - Efficacy Evaluable Population

[33] - Efficacy Evaluable Population

[34] - Efficacy Evaluable Population

[35] - Efficacy Evaluable Population

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[36]			
Units: weeks				
median (confidence interval 95%)	9999 (79.1 to 9999)			

Notes:

[36] - Efficacy Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Treatment-Emergent Adverse Events (TEAE)

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

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 42 days after the last dose. The severity of AEs was graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 and the scale: Grade 1 = Mild Grade 2 = Moderate Grade 3 = Severe Grade 4 = Life threatening Grade 5 = Death. Relation to study drug was determined by the investigator. A treatment-related TEAE is defined as TEAE which was considered to be related to the study drug and reported as 'Suspected' on the CRF. AEs with a missing relationship were treated as 'treatment-related' in data summaries.

End point type	Secondary
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End point timeframe:

Day 1 up to 59.2 months

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[37]	6 ^[38]	21 ^[39]	35 ^[40]
Units: participants				
>= 1 Treatment-emergent adverse event (TEAE)	6	4	20	34
>=1 Treatment-related TEAE	2	3	7	18
>=1 Serious TEAE	1	2	6	10
>=1 Serious TEAE related to treatment	0	0	0	0
>=1 TEAE severity 3 or 4	1	2	9	13
>=1 TEAE severity grade 3/4 related to treatment	0	0	1	0
>=1 TEAE leading to death	0	1	0	0
>=1 TEAE leading to dose reduction	0	0	0	0
>=1 TEAE leading to dose interruption	0	1	2	9
>=1 TEAE leading to dose interruption + reduction	0	0	0	1
>= 1 TEAE leading to drug discontinuation	0	2	2	3

Notes:

[37] - Safety population

[38] - Safety population

[39] - Safety population

[40] - Safety population

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[41]			
Units: participants				
>= 1 Treatment-emergent adverse event (TEAE)	5			
>=1 Treatment-related TEAE	4			
>=1 Serious TEAE	2			
>=1 Serious TEAE related to treatment	1			
>=1 TEAE severity 3 or 4	2			

>=1 TEAE severity grade 3/4 related to treatment	1			
>=1 TEAE leading to death	0			
>=1 TEAE leading to dose reduction	0			
>=1 TEAE leading to dose interruption	1			
>=1 TEAE leading to dose interruption + reduction	0			
>= 1 TEAE leading to drug discontinuation	2			

Notes:

[41] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Red Blood Cell (RBC)-Transfusion Independence During the Erythroid Hematological Improvement (HI-E) Interval

End point title	Percentage of Participants Who Achieved Red Blood Cell (RBC)-Transfusion Independence During the Erythroid Hematological Improvement (HI-E) Interval
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End point description:

Percentage of participants who achieved RBC-independence was defined as participants who required no RBC transfusions during a 56-day interval of erythroid hematological improvement (HI-E). NTDE = nontransfusion dependence efficacy participants who required < 4 units of RBCs in the 8 weeks prior to start of therapy TDE = transfusion dependence efficacy participants who required >=4 units of RBCs in the 8 weeks prior to start of therapy

End point type	Secondary
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End point timeframe:

Day 2 - 142

End point values	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg	Sotatercept 1.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7 ^[42]	6 ^[43]	21 ^[44]	35 ^[45]
Units: percent of participants				
number (not applicable)				
All subjects	0	1	3	15
NTDE subpopulation	0	0	1	6
TDE subpopulation	0	1	2	9

Notes:

[42] - All = 7 participants NTDE = 0 participants TDE = 7 participants

[43] - All = 6 participants NTDE = 0 participants TDE = 6 participants

[44] - All = 21 participants NTDE = 3 participants TDE = 18 participants

[45] - All = 35 participants NTDE = 8 participants TDE = 27 participants

End point values	Sotatercept 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[46]			
Units: percent of participants				

number (not applicable)				
All subjects	1			
NTDE subpopulation	1			
TDE subpopulation	0			

Notes:

[46] - All = 5 participants NTDE = 1 participants TDE = 4 participants

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 60.7 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Sotatercept 0.1 mg/kg
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Reporting group description:

Sotatercept 0.1 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.

Reporting group title	Sotatercept 0.3 mg/kg
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Reporting group description:

Sotatercept 0.3 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to either the 0.1 mg/kg arm or the 0.3 mg/kg arm. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/5$ subjects in Cycle 1 in the 0.1 mg/kg and 0.3 mg/kg treatment groups, the 0.5 mg/kg treatment group began inclusion in the randomization scheme.

Reporting group title	Sotatercept 0.5 mg/kg
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Reporting group description:

Sotatercept 0.5 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 0.5 mg/kg treatment group, the 1.0 mg/kg treatment group began inclusion in the randomization scheme.

Reporting group title	Sotatercept 1.0 mg/kg
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Reporting group description:

Sotatercept 1.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. Based upon the occurrence of dose-limiting toxicity (DLT) in $\leq 1/6$ subjects in Cycle 1 in the 1.0 mg/kg treatment group, the 2.0 mg/kg treatment group began inclusion in the randomization scheme. Following evaluation of all treatment group data by the Steering Committee, enrollment continued only in the 1.0 mg/kg arm because the arm had the greatest frequency of erythroid hematological improvement (HI-E).

Reporting group title	Sotatercept 2.0 mg/kg
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Reporting group description:

Sotatercept 2.0 mg/kg administered via subcutaneous injection every third week (Q3W). Participants were randomized to one of the active treatment arms. Efficacy and safety data were assessed by a Steering Committee. The 2.0 mg/kg sotatercept dose was reduced to 1.5 mg/kg for ongoing and newly enrolled participants by protocol amendment.

Serious adverse events	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	6 / 21 (28.57%)
number of deaths (all causes)	0	1	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (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
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mass			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Psychiatric disorders			

Delirium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
International normalised ratio increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Spinal fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Subdural haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transfusion reaction			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
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			
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Large intestine perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Cholelithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Escherichia pyelonephritis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (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
Lung infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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
Peritoneal abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (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 / 7 (0.00%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sotatercept 1.0 mg/kg	Sotatercept 2.0 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 35 (28.57%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mass			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			

subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			

subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritoneal abscess			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sotatercept 0.1 mg/kg	Sotatercept 0.3 mg/kg	Sotatercept 0.5 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	4 / 6 (66.67%)	18 / 21 (85.71%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	0	1	3
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	0	1	6
Chest discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	6 / 21 (28.57%)
occurrences (all)	0	9	13
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Injection site reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	6 / 21 (28.57%)
occurrences (all)	2	3	10
Peripheral swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 21 (19.05%)
occurrences (all)	0	1	4
Vessel puncture site swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	1	3	3
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	6 / 21 (28.57%)
occurrences (all)	0	1	7
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Insomnia			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 21 (4.76%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	3 / 21 (14.29%) 3
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	4 / 21 (19.05%) 4
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 21 (4.76%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0
Creatinine renal clearance decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 21 (9.52%) 2
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 21 (9.52%) 7
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Fall			

subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Muscle strain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	1 / 21 (4.76%)
occurrences (all)	1	3	1
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	4 / 21 (19.05%)
occurrences (all)	3	2	4
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Haemolytic anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	5
Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	8
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Eye inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Vitreous floaters			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	6 / 21 (28.57%)
occurrences (all)	0	1	7
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	7 / 21 (33.33%)
occurrences (all)	0	5	7
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 21 (19.05%)
occurrences (all)	0	2	4
Salivary gland enlargement			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Vomiting subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	3 / 21 (14.29%) 4
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Ecchymosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	1 / 21 (4.76%) 1
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 21 (9.52%) 2
Skin lesion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 21 (0.00%) 0
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 21 (9.52%) 2
Proteinuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 21 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	2 / 21 (9.52%) 2
Arthritis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 21 (4.76%) 1

Back pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Osteopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	0	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	5
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	0	1	2

Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Iron overload			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Non-serious adverse events	Sotatercept 1.0 mg/kg	Sotatercept 2.0 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 35 (91.43%)	5 / 5 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 35 (11.43%)	1 / 5 (20.00%)	
occurrences (all)	6	1	
Hypotension			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 35 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	28	0	
Chest discomfort			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Face oedema			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Fatigue			

subjects affected / exposed	11 / 35 (31.43%)	1 / 5 (20.00%)	
occurrences (all)	16	1	
Gait disturbance			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Injection site reaction			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Oedema			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	11 / 35 (31.43%)	0 / 5 (0.00%)	
occurrences (all)	19	0	
Peripheral swelling			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Vessel puncture site swelling			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	6 / 35 (17.14%)	1 / 5 (20.00%)	
occurrences (all)	6	1	
Dyspnoea			
subjects affected / exposed	2 / 35 (5.71%)	1 / 5 (20.00%)	
occurrences (all)	5	1	
Dyspnoea exertional			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	8	0	
Epistaxis			
subjects affected / exposed	8 / 35 (22.86%)	1 / 5 (20.00%)	
occurrences (all)	11	1	
Hypoxia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 35 (11.43%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Confusional state			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Insomnia			

subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	0 / 5 (0.00%) 0	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	0 / 5 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	0 / 5 (0.00%) 0	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 5 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	0 / 5 (0.00%) 0	
Blood creatinine increased subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 5	1 / 5 (20.00%) 1	
Creatinine renal clearance decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 5 (0.00%) 0	
Lipase increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 5 (0.00%) 0	
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 5 (20.00%) 2	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 5 (20.00%) 1	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 5 (0.00%) 0	
Fall			

subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences (all)	5	0	
Muscle strain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Spinal compression fracture			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Tooth fracture			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	6 / 35 (17.14%)	2 / 5 (40.00%)	
occurrences (all)	7	2	
Dysgeusia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	5 / 35 (14.29%)	1 / 5 (20.00%)	
occurrences (all)	8	1	
Paraesthesia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	5	0	
Haemolytic anaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Leukocytosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	4	4	
Thrombocytopenia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Eye inflammation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Lacrimation increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Vitreous floaters			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 5 (0.00%) 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	5 / 35 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	9	0	
Abdominal pain upper			
subjects affected / exposed	4 / 35 (11.43%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	9 / 35 (25.71%)	2 / 5 (40.00%)	
occurrences (all)	17	3	
Dry mouth			
subjects affected / exposed	2 / 35 (5.71%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	8 / 35 (22.86%)	2 / 5 (40.00%)	
occurrences (all)	15	2	
Salivary gland enlargement			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Toothache			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Vomiting subjects affected / exposed occurrences (all)	9 / 35 (25.71%) 14	1 / 5 (20.00%) 4	
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 5 (20.00%) 1	
Ecchymosis subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 5 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	0 / 5 (0.00%) 0	
Pruritus generalised subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 5 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	0 / 5 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 5 (0.00%) 0	
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 5 (0.00%) 0	
Proteinuria subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	0 / 5 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 8	0 / 5 (0.00%) 0	
Arthritis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 5 (20.00%) 1	

Back pain			
subjects affected / exposed	4 / 35 (11.43%)	1 / 5 (20.00%)	
occurrences (all)	7	2	
Muscle spasms			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Muscular weakness			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	1 / 35 (2.86%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Osteoarthritis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	7	0	
Osteopenia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	4 / 35 (11.43%)	1 / 5 (20.00%)	
occurrences (all)	16	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Laryngitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	4 / 35 (11.43%)	0 / 5 (0.00%)	
occurrences (all)	6	0	
Tooth infection			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 35 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	9	0	
Urinary tract infection			
subjects affected / exposed	4 / 35 (11.43%)	2 / 5 (40.00%)	
occurrences (all)	7	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 35 (22.86%)	1 / 5 (20.00%)	
occurrences (all)	10	1	
Dehydration			
subjects affected / exposed	3 / 35 (8.57%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Hypercalcaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Hyperkalaemia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 5 (20.00%)	
occurrences (all)	2	1	

Hyperuricaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Hypoglycaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Iron overload			
subjects affected / exposed	2 / 35 (5.71%)	1 / 5 (20.00%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2012	<p>- Revision of protocol title and inclusion criteria to reflect the inclusion of CMML as a subclassification of the MDS/ myeloproliferative neoplasms subgroup as outlined in protocol Appendix A. -Revision of the DLT criteria, including Rules for Delay, Reduction and Discontinuation of Treatment (protocol Table 8) and Reasons for Discontinuation for: a. Hemoglobin > 12 g/dL, sustained for ≥ 7 days, confirmed by 2 assessments ≥ 1 week apart. b. Hypertension Grade ≥ 2 according to NCI-CTCAE version 4.0 (current active minor version), BP values must be confirmed by 2 readings obtained 5 minutes apart. c. Treatment-related (suspected) toxicity Grade ≥ 3. - Clarification of definition of favorable safety profile as a safe, tolerable, and effective dose of sotatercept that results in the greatest frequency of HI-E in subjects with anemia and low- or int-1 risk MDS. - Addition of specific early stopping criteria for an excess number of DLTs or the absence of efficacy within a dose cohort - Revision of inclusion criteria to: a. Only allow subjects requiring RBC transfusions to be eligible for the study b. Add language that females of child-bearing potential must agree to use effective contraception while participating in this study c. Add pregnancy prevention language for males participating in this study - Revision of exclusion criteria to exclude subjects with uncontrolled hypertension (SBP > 140 mm Hg or DBP ≥ 90 mm Hg). Controlled hypertension for this protocol was considered Grade ≤ 1 according to NCI-CTCAE version 4.0 (current active minor version) - Revision of Rules for Delay, Reduction and Discontinuation of Treatment Section to: a. Clarify discontinuation due to treatment-related (suspected) toxicity Grade ≥ 3 b. Clarify discontinuation due to treatment-related (suspected) toxicity Grade ≤ 2 that delays treatment by more than 3 months c. Provide dose reduction guidance for subjects who experience a rapid rise in Hgb</p>
12 February 2013	<p>- Added clarification related to the hypertension DLT definition to ensure harmonization of DLT assessment for hypertension across all study sites due to unique attributes of the study population - Provided clear parameters for Extension Period eligibility to offer flexibility for those subjects who do not meet protocol-defined HI-E to enter the Extension Period, at the investigator's discretion, if clinical benefit was seen at the conclusion of the Treatment Period - Removed the Cycle 3 Day 1 mandatory MDS response assessment as it was deemed too soon after initiation of treatment of study drug - Continued to follow efficacy parameters (ie, Hgb and transfusions) for up to 3 months after the last dose of study drug or start of next treatment to assess potential late response after study drug discontinuation as was sometimes observed with ESAs - Modified the AE reporting period to 42 days after the last dose was administered. Beyond 42 days, all SAEs deemed suspected related to study drug will still be reported - Included chromosome del (5q) MDS patients who have failed on lenalidomide, intolerable to lenalidomide, or have other cytopenia precluding use of lenalidomide, as these patients could potentially benefit from treatment with sotatercept Increased the frequency of BP monitoring from once per cycle to weekly during the first 5 cycles of treatment, with the added flexibility of home monitoring - Addition of an Independent Cardiologist to the Steering Committee to focus on potential cardiovascular effects of the study drug - Increased the contraception use requirement for males after the last administration of study drug from 112 days to 7 months/210 days to account for the limited data on the study drug's effect on spermatogenesis - Agreement on additional language related to clarification of the hypertension DLT definition</p>

04 August 2013	<p>- Additional dose levels were added beyond 0.5 mg/kg cohort (ie, 1.0 mg/kg SC Q3W and 2.0 mg/kg SQ Q3W), as 0.5 mg/kg may be subtherapeutic in study population - Additional safety measure was added to ensure adequate data were available and reviewed by the Steering Committee prior to all future dose escalation - Additional safety measure was added to allow potential exploration of intermediate dose levels (eg, 0.75 mg/kg and 1.5 mg/kg) at time of dose escalation to 1.0 mg/kg and 2.0 mg/kg respectively upon Steering Committee review of safety and efficacy data - Additional dose reduction levels were added to account for additional dose levels added beyond 0.5 mg/kg - New text was added to provide guidance to sites when total volume of calculated dose exceeds what was typically administered in 1 SC injection - New text consistent with previous rationale added to "Rationale for Study Design" section to account for addition of dose levels beyond 0.5 mg/kg - New text added related to timing of Steering Committee meetings to account for additional dose levels beyond 0.5 mg/kg - Additional guidance related to predose Hgb level prior to Cycle 1 Day 1 treatment administration for subjects who were deemed NTDE per protocol was provided - New text was added related to Steering Committee guidance on closure of treatment group to further enrollment due to lack of efficacy to minimize number of patients enrolled at subtherapeutic doses after their review of safety and efficacy data - New text was added to account for varying operational logistics at study sites related to timing of availability of predose Hgb result - Clarification on HI-E definition for subjects who were classified as NTDE per protocol - Clarification was added that hypertension DLT was confirmed by study investigator/clinical site at the clinical site and not based solely on a measurement taken at home by the subject or caretaker</p>
03 August 2015	<p>- Subjects in the sotatercept 2.0 mg/kg dosing group were dose reduced to sotatercept 1.5 mg/kg. Subsequent enrollment into this dosing group was at sotatercept 1.5 mg/kg; however, no subjects were enrolled at the 1.5 mg/kg starting dose level. - Enrollment into Part 2 (expansion) commenced without delay at a sotatercept dose level of 1.0 mg/kg - Language was added to include the availability of a roll-over protocol for subjects that remained on study following the analysis of all key endpoints and objectives of the study - A request for historic MDS molecular mutational analysis data, if available, was added - Recently published preclinical data was added - Addition of references related to recently published preclinical data - Updated data from the completed ACE-011-NSCL-001 study was added - Updated incidence of antisotatercept antibody data was added</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29331635>