# 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 MYELODYSPLASTIC 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 |

**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 |

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 |

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 ≤ 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 |

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 ≤ 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 |

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 ≤ 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 ≤ 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 ≤ 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 ≤ 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<br>Units: Subjects | | | |
| <65 years | 3 | 0 | 7 |
| >=65 to <75 years | 2 | 3 | 8 |
| >=75 years | 2 | 3 | 6 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 67 | 75 | 69 |
| standard deviation | ± 8.3 | ± 6.9 | ± 8.0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 0 | 4 |

| | | | |
|---|---|---|---|
| Male | 4 | 6 | 17 |

| | | | |
|---|---|---|---|
| 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<br>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<br>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<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 2 |
| Not Hispanic or Latino | 7 | 6 | 13 |
| Missing | 0 | 0 | 6 |
| Erythropoietin Level<br>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<br>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<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 2 |
| Not Hispanic or Latino | 19 | 4 | 49 |
| Missing | 16 | 1 | 23 |
| Erythropoietin Level<br>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<br>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<br>Units: cm | | | |
| arithmetic mean | 1.68 | 1.56 | |
| standard deviation | ± 0.089 | ± 0.043 | - |
| Weight<br>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 ≤ 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 ≤ 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 ≤ 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 ≤ 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. >= 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.>= 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.>= 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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: • >=50% increase in blasts • >=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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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: • >=50% increase in blasts • >=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 |
|---|---|

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 | | | |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 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) |

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 |

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) |
|---|---|

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 |
|---|---|

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 |

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 = nonntransfusion 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 |

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### 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 ≤ 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 ≤ 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 ≤ 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 ≤ 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.

| 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 | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 0 | 3 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 4 / 21 (19.05%) |
| occurrences (all) | 0 | 0 | 4 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 7 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 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 | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 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 | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 3 / 21 (14.29%) |
| occurrences (all) | 0 | 1 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 6 (16.67%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 1 | 1 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 1 / 21 (4.76%) |
| occurrences (all) | 0 | 0 | 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 | 3 / 35 (8.57%) | 0 / 5 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 5 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 0 / 5 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 5 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 5 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 5 (20.00%) | |
| occurrences (all) | 5 | 1 | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 2 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 5 (0.00%) | |
| occurrences (all) | 2 | 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 | 0 / 35 (0.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 0 | 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 | 9 / 35 (25.71%) | 1 / 5 (20.00%) | |
| occurrences (all) | 14 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 1 | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 5 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 5 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rash | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 5 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 5 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 5 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 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 | - 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 ..... |
| 12 February 2013 | - 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 .... |

| | |
|---|---|
| 04 August 2013 | - 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 .... |
| 03 August 2015 | - 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 |

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