



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2020-004142-11 |
| Trial protocol | DE SE FR BE NL AT PL CZ IT |
| Global end of trial date | 06 December 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 26 November 2023 |
| First version publication date | 26 November 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 7962-003 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04576988 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck: MK-7962-003 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme LLC |
| Sponsor organisation address | 126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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 | 06 December 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 August 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 December 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are to evaluate the efficacy and safety of sotatercept (MK-7962) treatment (plus background pulmonary arterial hypertension (PAH) therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH. The primary hypothesis of the study is that the participants receiving sotatercept will have improved 6-minute walk distance (6MWD) at 24 weeks compared to participants receiving placebo.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Background pulmonary arterial hypertension (PAH) therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 25 January 2021 |
| 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 | Argentina: 2 |
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Brazil: 26 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Czechia: 5 |
| Country: Number of subjects enrolled | France: 30 |
| Country: Number of subjects enrolled | Germany: 71 |
| Country: Number of subjects enrolled | Israel: 9 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Mexico: 8 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Poland: 22 |
| Country: Number of subjects enrolled | Serbia: 2 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | United States: 88 |
| Worldwide total number of subjects | 323 |
| EEA total number of subjects | 161 |

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) | 269 |
| From 65 to 84 years | 54 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Of the 324 randomized participants, 1 participant was randomized in error and did not receive study treatment and no data was collected. Hence, the results are presented on 323 participants.

Pre-assignment

Screening details:

Per protocol, not all participants from the double-blind placebo controlled (DBPC) period entered the long-term double blind (LTDB) period due to clinical worsening or consent withdrawal after DBPC period.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double Blind Placebo Controlled (DBPC) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Sotatercept plus background PAH therapy |

Arm description:

Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the double-blind placebo controlled (DBPC) period for up to approximately 24 weeks. After 24 weeks, participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the long-term double blind (LTDB) period for up to approximately 72 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Background PAH Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Inhalation solution, Powder for injection |
| Routes of administration | Subcutaneous use, Oral use, Inhalation use, Intravenous use |

Dosage and administration details:

Background PAH therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | MK-7962 ACE-011 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously (SC) every 21 days plus background PAH therapy.

| | |
|------------------|-------------------------------------|
| Arm title | Placebo plus background PAH therapy |
|------------------|-------------------------------------|

Arm description:

Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks and the LTDB period for up to approximately 72 weeks.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Placebo administered subcutaneously (SC) every 21 days plus background PAH therapy. | |
| Investigational medicinal product name | Background PAH Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Inhalation solution, Powder for injection |
| Routes of administration | Subcutaneous use, Oral use, Inhalation use, Intravenous use |
| Dosage and administration details: | |
| Background PAH therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist. | |

| Number of subjects in period 1 | Sotatercept plus background PAH therapy | Placebo plus background PAH therapy |
|--------------------------------|---|-------------------------------------|
| Started | 163 | 160 |
| Treated | 163 | 160 |
| Completed | 159 | 148 |
| Not completed | 4 | 12 |
| Adverse event, serious fatal | - | 5 |
| Consent withdrawn by subject | 2 | 3 |
| Adverse event, non-fatal | 1 | 1 |
| Clinical worsening event | - | 2 |
| Protocol deviation | 1 | 1 |

| | |
|------------------------------|--|
| Period 2 | |
| Period 2 title | Long Term Double Blind (LTDB) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |
| Arms | |
| Are arms mutually exclusive? | Yes |

| | |
|------------------|---|
| Arm title | Sotatercept plus background PAH therapy |
|------------------|---|

Arm description:

Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the double-blind placebo controlled (DBPC) period for up to approximately 24 weeks. After 24 weeks, participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the long-term double blind (LTDB) period for up to approximately 72 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Background PAH Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Inhalation solution, Powder for injection |
| Routes of administration | Oral use, Inhalation use, Subcutaneous use, Intravenous use |

Dosage and administration details:

Background PAH therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Sotatercept |
| Investigational medicinal product code | |
| Other name | MK-7962 ACE-011 |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously (SC) every 21 days plus background PAH therapy.

| | |
|------------------|-------------------------------------|
| Arm title | Placebo plus background PAH therapy |
|------------------|-------------------------------------|

Arm description:

Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks and the LTDB period for up to approximately 72 weeks.

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

Dosage and administration details:

Placebo administered subcutaneously (SC) every 21 days plus background PAH therapy.

| | |
|--|---|
| Investigational medicinal product name | Background PAH Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Inhalation solution, Powder for injection |
| Routes of administration | Oral use, Inhalation use, Subcutaneous use, Intravenous use |

Dosage and administration details:

Background PAH therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

| Number of subjects in period 2^[1] | Sotatercept plus background PAH therapy | Placebo plus background PAH therapy |
|---|--|--|
| Started | 159 | 142 |
| Treated | 158 | 142 |
| Completed | 155 | 136 |
| Not completed | 4 | 6 |
| Adverse event, serious fatal | 2 | 1 |
| Consent withdrawn by subject | - | 3 |
| Adverse event, non-fatal | 2 | - |
| Sponsor decision | - | 1 |
| Protocol deviation | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants entered LTDB period.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Sotatercept plus background PAH therapy |
| Reporting group description: | |
| Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the double-blind placebo controlled (DBPC) period for up to approximately 24 weeks. After 24 weeks, participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the long-term double blind (LTDB) period for up to approximately 72 weeks. | |
| Reporting group title | Placebo plus background PAH therapy |
| Reporting group description: | |
| Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks and the LTDB period for up to approximately 72 weeks. | |

| Reporting group values | Sotatercept plus background PAH therapy | Placebo plus background PAH therapy | Total |
|--|---|-------------------------------------|-------|
| Number of subjects | 163 | 160 | 323 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 47.6 | 48.3 | |
| standard deviation | ± 14.09 | ± 15.50 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 129 | 127 | 256 |
| Male | 34 | 33 | 67 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 1 | 6 | 7 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 2 | 5 | 7 |
| White | 147 | 141 | 288 |
| More than one race | 7 | 4 | 11 |
| Unknown or Not Reported | 6 | 2 | 8 |
| Ethnicity (NIH/OMB) | | | |

| | | | |
|---|---------|---------|-----|
| Units: Subjects | | | |
| Hispanic or Latino | 27 | 31 | 58 |
| Not Hispanic or Latino | 132 | 124 | 256 |
| Unknown or Not Reported | 4 | 5 | 9 |
| World Health Organization (WHO) functional class (FC) II or III at baseline | | | |
| WHO FC was used to rate how ill a pulmonary arterial hypertension (PAH) participant was. Class II: Participants with PAH resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class III: Participants with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope | | | |
| Units: Subjects | | | |
| Class II | 79 | 78 | 157 |
| Class III | 84 | 82 | 166 |
| Background PAH Therapy at Baseline | | | |
| Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy (double or triple therapy) with endothelin-receptor antagonist (ERA), a phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. | | | |
| Units: Subjects | | | |
| Monotherapy | 9 | 4 | 13 |
| Double therapy | 56 | 56 | 112 |
| Triple therapy | 98 | 100 | 198 |
| 6-Minute Walk Distance (6MWD) at baseline | | | |
| The 6MWD is the distance walked in 6 minutes as a measure of functional capacity. | | | |
| Units: meters | | | |
| arithmetic mean | 397.6 | 404.7 | |
| standard deviation | ± 84.28 | ± 80.59 | - |

Subject analysis sets

| | |
|--|---|
| Subject analysis set title | Sotatercept plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Sotatercept plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DPBC period) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks.

| | |
|----------------------------|---|
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks.

| Reporting group values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | Sotatercept plus background PAH therapy (DBPC period) |
|---|---|---|---|
| Number of subjects | 163 | 160 | 162 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 34.4 | 1.0 | 38.9 |
| standard deviation | ± | ± | ± |
| Sex: Female, Male Units: Participants | | | |
| Female | | | |
| Male | | | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported | | | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported | | | |
| World Health Organization (WHO) functional class (FC) II or III at baseline | | | |
| WHO FC was used to rate how ill a pulmonary arterial hypertension (PAH) participant was. Class II: Participants with PAH resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class III: | | | |

| | | | |
|--|------|-----|------|
| Participants with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope | | | |
| Units: Subjects | | | |
| Class II | | | |
| Class III | | | |
| Background PAH Therapy at Baseline | | | |
| Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy (double or triple therapy) with endothelin-receptor antagonist (ERA), a phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. | | | |
| Units: Subjects | | | |
| Monotherapy | | | |
| Double therapy | | | |
| Triple therapy | | | |
| 6-Minute Walk Distance (6MWD) at baseline | | | |
| The 6MWD is the distance walked in 6 minutes as a measure of functional capacity. | | | |
| Units: meters | | | |
| arithmetic mean | 34.4 | 1.0 | 38.9 |
| standard deviation | ± | ± | ± |

| Reporting group values | Placebo plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DPBC period) | Placebo plus background PAH therapy (DBPC period) |
|--|---|---|---|
| Number of subjects | 159 | 160 | 160 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 10.1 | 58.6 | 0.01 |
| standard deviation | ± | ± | ± |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | | | |
| Male | | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | | | |
| Asian | | | |
| Native Hawaiian or Other Pacific Islander | | | |
| Black or African American | | | |
| White | | | |

| | | | |
|---|------|------|------|
| More than one race Unknown or Not Reported | | | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported | | | |
| World Health Organization (WHO) functional class (FC) II or III at baseline | | | |
| WHO FC was used to rate how ill a pulmonary arterial hypertension (PAH) participant was. Class II: Participants with PAH resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. Class III: Participants with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope | | | |
| Units: Subjects | | | |
| Class II Class III | | | |
| Background PAH Therapy at Baseline | | | |
| Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy (double or triple therapy) with endothelin-receptor antagonist (ERA), a phosphodiesterase 5 (PDE5) inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists. | | | |
| Units: Subjects | | | |
| Monotherapy Double therapy Triple therapy | | | |
| 6-Minute Walk Distance (6MWD) at baseline | | | |
| The 6MWD is the distance walked in 6 minutes as a measure of functional capacity. | | | |
| Units: meters | | | |
| arithmetic mean | 10.1 | 58.6 | 0.01 |
| standard deviation | ± | ± | ± |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Sotatercept plus background PAH therapy |
| Reporting group description: Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the double-blind placebo controlled (DBPC) period for up to approximately 24 weeks. After 24 weeks, participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the long-term double blind (LTDB) period for up to approximately 72 weeks. | |
| Reporting group title | Placebo plus background PAH therapy |
| Reporting group description: Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks and the LTDB period for up to approximately 72 weeks. | |
| Reporting group title | Sotatercept plus background PAH therapy |
| Reporting group description: Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the double-blind placebo controlled (DBPC) period for up to approximately 24 weeks. After 24 weeks, participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the long-term double blind (LTDB) period for up to approximately 72 weeks. | |
| Reporting group title | Placebo plus background PAH therapy |
| Reporting group description: Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks and the LTDB period for up to approximately 72 weeks. | |
| Subject analysis set title | Sotatercept plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received dose matched placebo by SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Sotatercept plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DPBC period) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks. | |
| Subject analysis set title | Placebo plus background PAH therapy (DBPC period) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks.

Primary: Change From Baseline in 6-Minute Walk Distance (6MWD) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in 6-Minute Walk Distance (6MWD) at Week 24 |
|-----------------|--|

End point description:

The 6MWD was the distance walked in 6 minutes as a measure of functional capacity. This was assessed using the 6-minute walk test (6MWT). Per protocol, change from baseline in 6MWD at Week 24 was reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and had a baseline value of 6MWD.

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

End point timeframe:

Baseline and Week 24

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: meters | | | | |
| median (full range (min-max)) | 34.4 (32.5 to 35.5) | 1.0 (-1.0 to 5.0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 ^[1] |
| Method | Aligned Rank Stratified Wilcoxon (ARSW) |
| Parameter estimate | Treatment difference |
| Point estimate | 40.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 27.53 |
| upper limit | 54.14 |

Notes:

[1] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Primary: Number of Participants Who Experienced an Adverse Event (AE)

| | |
|-----------------|---|
| End point title | Number of Participants Who Experienced an Adverse Event |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in a study participant administered a study drug, which did not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it was considered related to the study drug. Per protocol, the number of participants who reported an AE were reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 24 weeks

Notes:

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

Justification: There was no statistical analysis planned for this endpoint.

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Participants | 138 | 140 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Study Treatment Due to an AE

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Treatment Due to an AE ^[3] |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in a study participant administered a study drug, which did not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it was considered related to the study drug. Per protocol, the number of participants who discontinued study treatment due to an AE were reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment.

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

End point timeframe:

Up to approximately 24 weeks

Notes:

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

Justification: There was no statistical analysis planned for this endpoint.

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Participants | 3 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Percentage of Participants Achieving Multicomponent Improvement at Week 24

| | |
|--|--|
| End point title | Change From Baseline in the Percentage of Participants Achieving Multicomponent Improvement at Week 24 |
| End point description: | |
| Multicomponent Improvement was defined as consisting of all of the following: (a) Improvement in 6MWD (increase ≥ 30 meters) (b) Improvement in N-terminal pro b-type natriuretic peptide (NT-proBNP; decrease in NT-proBNP $\geq 30\%$) or maintenance/achievement of NT-proBNP level < 300 ng/L (c) Improvement in World Health Organization (WHO) Functional Class (FC) or maintenance of WHO FC II. Per protocol, change from baseline in the percentage of participants achieving multicomponent improvement at Week 24 was reported for DBPC period. The analysis population included All randomized participants who received at least one dose of study treatment and who had a baseline measurement for the multicomponent improvement. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 162 | 159 | | |
| Units: Percent change | | | | |
| number (not applicable) | 38.9 | 10.1 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Probability of multicomponent improvement |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 321 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 ^[4] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[4] - A 2-sided p-value was calculated using Cochran-Mantel-Haenszel (CMH) method with WHO FC II/III and background PAH therapy as strata.

Secondary: Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 24 |
|-----------------|--|

End point description:

PVR is a hemodynamic variable of pulmonary circulation and was measured by right heart catheterization (RHC). Per protocol, the change from baseline in PVR at Week 24 was reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and who had a baseline measurement for the PVR.

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

End point timeframe:

Baseline and Week 24

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|----------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: dynes*sec/cm ⁵ | | | | |
| median (full range (min-max)) | -165.1 (-184.0 to -152.0) | 32.8 (24.0 to 40.0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 ^[5] |
| Method | ARSW test |
| Parameter estimate | Treatment difference |
| Point estimate | -234.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -288.37 |
| upper limit | -180.75 |

Notes:

[5] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Secondary: Change From Baseline in NT-proBNP Levels at Week 24

| | |
|---|---|
| End point title | Change From Baseline in NT-proBNP Levels at Week 24 |
| End point description: NT-proBNP is a circulating biomarker that reflects myocardial stretch. Per protocol, the change from baseline in NT-proBNP level at Week 24 was reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and who had a baseline measurement for the NT-proBNP levels. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 24 | |

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DPBC period) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: pg/mL | | | | |
| median (full range (min-max)) | -230.3 (-236.0 to -223.0) | 58.6 (44.0 to 73.0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Treatment Difference |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DPBC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 ^[6] |
| Method | ARSW test |
| Parameter estimate | Treatment difference |
| Point estimate | -441.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -573.54 |
| upper limit | -309.61 |

Notes:

[6] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Secondary: Change From Baseline in the Percentage of Participants Who Improve in WHO FC at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in the Percentage of Participants Who |
|-----------------|--|

End point description:

The severity of participant's pulmonary arterial hypertension (PAH) symptoms will be graded using the WHO FC system. WHO functional classification for PAH ranges from Class I (no limitation in physical activity, no dyspnea with normal activity), Class II (slight limitation of physical activity), Class III (marked limitation of physical activity) and Class IV (cannot perform a physical activity without any symptoms, dyspnea at rest). Participants who improve in WHO FC were classified into "Improved", "No change" and "Worsened". Improvement = reduction in FC, worsened = increase in FC and no change = no change in FC. Per protocol, change from baseline in the percentage of participants who improve in WHO FC at Week 24 were reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and who had a baseline measurement for the WHO FC.

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

End point timeframe:

Baseline and Week 24

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 159 | | |
| Units: Percent change | | | | |
| number (not applicable) | 29.4 | 13.8 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Probability of who improve in WHO FC |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 322 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Time to Death or the First Occurrence of Clinical Worsening Event

| | |
|-----------------|---|
| End point title | Time to Death or the First Occurrence of Clinical Worsening Event |
|-----------------|---|

End point description:

Clinical Worsening events are defined as any of the following: worsening-related listing for lung and/or heart transplant; need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more; need for atrial septostomy; hospitalization for worsening of PAH (≥ 24 hours); or deterioration of PAH defined by both of the following events occurring at any time: worsened WHO FC and decrease in 6MWD by $\geq 15\%$ confirmed by 2 tests at least 4 hours apart, but no more than 1 week. Per protocol, time to death or the first occurrence of clinical worsening event was reported. The analysis population included all randomized participants who received at least one dose of study treatment and who died or experienced a first clinical worsening event.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 18 months | |

| End point values | Sotatercept plus background PAH therapy | Placebo plus background PAH therapy | | |
|-----------------------------|---|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Weeks | | | | |
| median (standard deviation) | 9999 (± 9999) | 9999 (± 9999) | | |

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|---|
| Comparison groups | Sotatercept plus background PAH therapy v Placebo plus background PAH therapy |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.163 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.076 |
| upper limit | 0.347 |

Secondary: Change From Baseline in Percentage of Participants Who Maintain or Achieve a Low Risk Score Using the Simplified French Risk Score Calculator at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Percentage of Participants Who Maintain or Achieve a Low Risk Score Using the Simplified French Risk Score Calculator at Week 24 |
|-----------------|--|

End point description:

The simplified French risk scoring system was based on the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension (PH). In this study, the noninvasive parameters were used to determine the score. 'Low risk' was defined as attaining or maintaining all 3 low-risk criteria: WHO FC I or II, 6MWD > 440 m, and NT-proBNP <300 ng/L. Per protocol, change from baseline in percentage of participants who maintained or achieved a low risk score using the simplified French risk score calculator at Week 24 was reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and who had a baseline measurement for the low risk score.

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

End point timeframe:
Baseline and Week 24

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 162 | 159 | | |
| Units: Percent Change | | | | |
| number (not applicable) | 39.5 | 18.2 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Probability |
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 321 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Change From Baseline in the Physical Impacts Domain Score of Pulmonary Arterial Hypertension - Symptoms and Impact (PAH-SYMPACT®) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in the Physical Impacts Domain Score of Pulmonary Arterial Hypertension - Symptoms and Impact (PAH-SYMPACT®) at Week 24 |
|-----------------|--|

End point description:

The PAH SYMPACT is a 23-item questionnaire to measure pulmonary arterial hypertension (PAH)-related symptoms and impact of PAH on daily life. The physical impact domain consists of walking slowly on flat surface, walking quickly on flat surface, walking uphill, carrying things, doing light indoor household chores, washing, or dressing oneself, and needing help from others. Participants were asked to recall and report on each item experienced in past 7 days. Each item score ranges from 0 (not difficult at all) to 4 (extremely difficult). Domain score was calculated by summing individual responses for each item and dividing by number of impact items (range: 0=no physical impact to 4=severe physical impact). Higher score indicated more severe physical impact. Change from baseline in physical impacts domain score at Week 24 was reported for DBPC period. Analysis population included all randomized participants who received at least 1 dose of study treatment and had baseline domain score.

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

End point timeframe:

Baseline and Week 24

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Score on a scale | | | | |
| median (full range (min-max)) | -0.13 (-0.15 to 0.00) | 0.01 (0.00 to 0.14) | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.01 ^[7] |
| Method | ARSW test |
| Parameter estimate | Treatment difference |
| Point estimate | -0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | -0.04 |

Notes:

[7] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Secondary: Change From Baseline in the Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT® at Week 24

| | |
|------------------------|---|
| End point title | Change From Baseline in the Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT® at Week 24 |
| End point description: | <p>The PAH SYMPACT is a 23-item questionnaire to measure PAH-related symptoms and impact of PAH on daily life. The cardiopulmonary symptoms consist of shortness of breath, fatigue, lack of energy, swelling in the ankles or legs, swelling in the stomach area, and cough. Participants were asked to recall and report on each item experienced in past 7 days. Each item score ranges from 0 (no symptom at all) to 4 (very severe symptoms). Mean individual symptom item score was determined for each of the 6 items and a domain score was calculated by summing the mean individual symptom item scores and dividing by the number of items (range: 0=no cardiopulmonary symptoms to 4=severe cardiopulmonary symptoms). Higher score indicated more severe symptoms experienced. Change from baseline in the cardiopulmonary domain score at Week 24 was reported for DBPC period. Analysis population included all randomized participants who received at least 1 dose of study treatment and had a baseline domain score.</p> |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Score on a scale | | | | |
| median (full range (min-max)) | -0.12 (-0.14 to -0.06) | -0.01 (-0.03 to 0.02) | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.028 ^[8] |
| Method | ARSW test |
| Parameter estimate | Treatment difference |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.256 |
| upper limit | -0.014 |

Notes:

[8] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Secondary: Change From Baseline in the Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT® at Week 24

| | |
|------------------------|---|
| End point title | Change From Baseline in the Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT® at Week 24 |
| End point description: | The PAH SYMPACT is a 23-item questionnaire to measure PAH-related symptoms and impact of PAH on daily life. The Cognitive/Emotional Impact domain consists of thinking clearly, feeling sad, feeling worried, and feeling frustrated. Participants were asked to recall and report on each item experienced in past 7 days. Score for each item ranges from 0 (not difficult at all) to 4 (extremely difficult). A domain score was calculated by summing the individual responses for each item and dividing by the number of impact items (range: 0=no cognitive/emotional impact to 4=severe cognitive/emotional impact). A higher score indicated more severe cognitive/emotional impact. Per protocol, change from baseline in the cognitive/emotional impacts domain score at Week 24 was reported for DBPC period. The analysis population included all randomized participants who received at least one dose of study treatment and who had a baseline cognitive/emotional impacts domain score. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | Sotatercept plus background PAH therapy (DBPC period) | Placebo plus background PAH therapy (DBPC period) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 160 | | |
| Units: Score on a scale | | | | |
| median (full range (min-max)) | 0.00 (0.00 to 0.00) | 0.000007 (0.00 to 0.0006) | | |

Statistical analyses

| Statistical analysis title | Treatment Difference |
|---|---|
| Comparison groups | Sotatercept plus background PAH therapy (DBPC period) v Placebo plus background PAH therapy (DBPC period) |
| Number of subjects included in analysis | 323 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.156 ^[9] |
| Method | ARSW test |
| Parameter estimate | Treatment difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.399 |
| upper limit | 0.084 |

Notes:

[9] - A 2-sided p-value was calculated using ARSW test with WHO FC II/III and background PAH therapy as strata.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 19 months

Adverse event reporting additional description:

All-cause mortality was reported on all randomized participants. Serious and non-serious adverse events were reported on all randomized participants who received at least one dose of study treatment. Mortality and safety were reported separately for the DBPC and LTDB periods.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Sotatercept Plus Background PAH Therapy (DBPC Period) |
|-----------------------|---|

Reporting group description:

Participants received a starting dose of sotatercept 0.3 mg/kg titrated up to 0.7mg/kg by subcutaneous (SC) injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks.

| | |
|-----------------------|---|
| Reporting group title | Placebo Plus Background PAH Therapy (LTDB Period) |
|-----------------------|---|

Reporting group description:

Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the LTDB period for up to approximately 72 weeks.

| | |
|-----------------------|---|
| Reporting group title | Sotatercept Plus Background PAH Therapy (LTDB Period) |
|-----------------------|---|

Reporting group description:

Participants received sotatercept dose titrated up to 0.7mg/kg SC injection every 21 days plus background PAH therapy during the LTDB period for up to approximately 72 weeks.

| | |
|-----------------------|---|
| Reporting group title | Placebo Plus Background PAH Therapy (DBPC Period) |
|-----------------------|---|

Reporting group description:

Participants received dose matched placebo SC injection every 21 days plus background PAH therapy during the DBPC period for up to approximately 24 weeks.

| Serious adverse events | Sotatercept Plus Background PAH Therapy (DBPC Period) | Placebo Plus Background PAH Therapy (LTDB Period) | Sotatercept Plus Background PAH Therapy (LTDB Period) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 163 (14.11%) | 14 / 142 (9.86%) | 26 / 158 (16.46%) |
| number of deaths (all causes) | 0 | 1 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Breast cancer | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device occlusion | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 2 / 158 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcoidosis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary artery aneurysm | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 142 (1.41%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Product issues | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Device physical property issue | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device leakage | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Myocardial necrosis marker increased | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| 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 | | | |
| Neck injury | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Joint injury | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 arrest | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 142 (0.70%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 failure acute | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Dizziness | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 2 / 158 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 polyp | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| 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 | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 142 (0.70%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Nephritis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Sjogren's syndrome | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Catheter site infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 2 / 158 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 2 / 158 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Oesophageal candidiasis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Perineal abscess | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 2 / 158 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Post-acute COVID-19 syndrome | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Sepsis syndrome | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| 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 device infection | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 1 / 158 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Hypervolaemia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 2 / 142 (1.41%) | 0 / 158 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 0 / 142 (0.00%) | 0 / 158 (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 |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 142 (0.70%) | 0 / 158 (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 |

| | | | |
|---|--|--|--|
| Serious adverse events | Placebo Plus Background PAH Therapy (DBPC Period) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 160 (22.50%) | | |
| number of deaths (all causes) | 6 | | |

| | | | |
|---|-----------------|--|--|
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Embolism venous | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Complication associated with device | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device occlusion | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary artery aneurysm | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 2 / 160 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | | |
|---|-----------------|--|--|--|
| Interstitial lung disease | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory distress syndrome | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 2 / 160 (1.25%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea exertional | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 160 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device physical property issue | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device leakage | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial necrosis marker | | | |

| | | | |
|---|-----------------|--|--|
| increased | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Neck injury | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 160 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |

| | | | | |
|---|-----------------|--|--|--|
| Atrial flutter | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiogenic shock | | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac failure acute | | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute coronary syndrome | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stress cardiomyopathy | | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Right ventricular failure | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 160 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroduodenal ulcer | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Urticaria | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephritis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Sjogren's syndrome | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemarthrosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 160 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perineal abscess | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post-acute COVID-19 syndrome | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypervolaemia | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 160 (0.63%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypovolaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 160 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Sotatercept Plus Background PAH Therapy (DBPC Period) | Placebo Plus Background PAH Therapy (LTDB Period) | Sotatercept Plus Background PAH Therapy (LTDB Period) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 111 / 163 (68.10%) | 50 / 142 (35.21%) | 82 / 158 (51.90%) |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 9 / 163 (5.52%) | 2 / 142 (1.41%) | 2 / 158 (1.27%) |
| occurrences (all) | 10 | 2 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 163 (10.43%) | 7 / 142 (4.93%) | 6 / 158 (3.80%) |
| occurrences (all) | 20 | 7 | 6 |
| Headache | | | |
| subjects affected / exposed | 33 / 163 (20.25%) | 6 / 142 (4.23%) | 9 / 158 (5.70%) |
| occurrences (all) | 41 | 7 | 9 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 163 (4.91%) | 0 / 142 (0.00%) | 8 / 158 (5.06%) |
| occurrences (all) | 9 | 0 | 9 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 17 / 163 (10.43%) | 4 / 142 (2.82%) | 10 / 158 (6.33%) |
| occurrences (all) | 20 | 4 | 12 |
| Injection site pain | | | |
| subjects affected / exposed | 11 / 163 (6.75%) | 1 / 142 (0.70%) | 0 / 158 (0.00%) |
| occurrences (all) | 12 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 163 (4.91%) | 3 / 142 (2.11%) | 6 / 158 (3.80%) |
| occurrences (all) | 10 | 3 | 7 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| Nausea subjects affected / exposed occurrences (all) | 17 / 163 (10.43%) 25 | 3 / 142 (2.11%) 5 | 8 / 158 (5.06%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 20 / 163 (12.27%) 21 | 3 / 142 (2.11%) 4 | 6 / 158 (3.80%) 7 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 3 / 163 (1.84%) 4 | 6 / 142 (4.23%) 7 | 2 / 158 (1.27%) 2 |
| Epistaxis subjects affected / exposed occurrences (all) | 20 / 163 (12.27%) 24 | 1 / 142 (0.70%) 5 | 25 / 158 (15.82%) 36 |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 9 / 163 (5.52%) 10 | 2 / 142 (1.41%) 2 | 5 / 158 (3.16%) 6 |
| Telangiectasia subjects affected / exposed occurrences (all) | 17 / 163 (10.43%) 21 | 2 / 142 (1.41%) 4 | 12 / 158 (7.59%) 16 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 24 / 163 (14.72%) 25 | 21 / 142 (14.79%) 21 | 24 / 158 (15.19%) 24 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 163 (4.29%) 9 | 5 / 142 (3.52%) 5 | 4 / 158 (2.53%) 4 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 163 (3.07%) 5 | 3 / 142 (2.11%) 3 | 8 / 158 (5.06%) 8 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 9 / 163 (5.52%) 9 | 1 / 142 (0.70%) 1 | 6 / 158 (3.80%) 7 |
| Iron deficiency | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 163 (1.23%) | 3 / 142 (2.11%) | 9 / 158 (5.70%) |
| occurrences (all) | 2 | 3 | 9 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | Placebo Plus Background PAH Therapy (DBPC Period) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 88 / 160 (55.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 3 / 160 (1.88%) | | |
| occurrences (all) | 5 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 160 (1.88%) | | |
| occurrences (all) | 4 | | |
| Headache | | | |
| subjects affected / exposed | 24 / 160 (15.00%) | | |
| occurrences (all) | 30 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 160 (1.88%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 160 (7.50%) | | |
| occurrences (all) | 12 | | |
| Injection site pain | | | |
| subjects affected / exposed | 10 / 160 (6.25%) | | |
| occurrences (all) | 12 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 160 (6.25%) | | |
| occurrences (all) | 10 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 17 / 160 (10.63%) | | |
| occurrences (all) | 26 | | |
| Diarrhoea | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 12 / 160 (7.50%) 13 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) | 12 / 160 (7.50%) 15 3 / 160 (1.88%) 3 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Telangiectasia subjects affected / exposed occurrences (all) | 4 / 160 (2.50%) 5 5 / 160 (3.13%) 5 | | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 19 / 160 (11.88%) 19 9 / 160 (5.63%) 10 3 / 160 (1.88%) 4 | | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Iron deficiency subjects affected / exposed occurrences (all) | 5 / 160 (3.13%) 5 7 / 160 (4.38%) 7 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 06 October 2021 | The major change for AM1 is to clarify that the Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domains of the PAH-SYMPACT will be evaluated as the secondary endpoints and EQ-5D-5L was removed as the secondary endpoint, removed hematology results requirement prior to study treatment, removed diuretics" from the description of background PAH therapy.06-Oct-2021 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported