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

End point title	Number of Participants Who Experienced an Adverse Event (AE)[1]

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:

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

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:

[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	3	10		

Statistical analyses

No statistical analyses for this end point

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 [3]
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:

[3] - 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 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 [4]
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:

[4] - 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 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 ≥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 [5]
Method	Cochran-Mantel-Haenszel

Notes:

[5] - 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 the Percentage of Participants Who Improve in WHO FC at Week 24

End point title	Change From Baseline in the Percentage of Participants Who Improve in WHO FC at Week 24

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: 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: 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 ≥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:

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.

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	17 / 163 (10.43%)	3 / 142 (2.11%)	8 / 158 (5.06%)
occurrences (all)	25	5	11
Diarrhoea			
subjects affected / exposed	20 / 163 (12.27%)	3 / 142 (2.11%)	6 / 158 (3.80%)
occurrences (all)	21	4	7
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 163 (1.84%)	6 / 142 (4.23%)	2 / 158 (1.27%)
occurrences (all)	4	7	2
Epistaxis			
subjects affected / exposed	20 / 163 (12.27%)	1 / 142 (0.70%)	25 / 158 (15.82%)
occurrences (all)	24	5	36
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 163 (5.52%)	2 / 142 (1.41%)	5 / 158 (3.16%)
occurrences (all)	10	2	6
Telangiectasia			
subjects affected / exposed	17 / 163 (10.43%)	2 / 142 (1.41%)	12 / 158 (7.59%)
occurrences (all)	21	4	16
Infections and infestations			
COVID-19			
subjects affected / exposed	24 / 163 (14.72%)	21 / 142 (14.79%)	24 / 158 (15.19%)
occurrences (all)	25	21	24
Nasopharyngitis			
subjects affected / exposed	7 / 163 (4.29%)	5 / 142 (3.52%)	4 / 158 (2.53%)
occurrences (all)	9	5	4
Urinary tract infection			
subjects affected / exposed	5 / 163 (3.07%)	3 / 142 (2.11%)	8 / 158 (5.06%)
occurrences (all)	5	3	8
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 163 (5.52%)	1 / 142 (0.70%)	6 / 158 (3.80%)
occurrences (all)	9	1	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	12 / 160 (7.50%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 160 (7.50%)		
occurrences (all)	15		
Epistaxis			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 160 (2.50%)		
occurrences (all)	5		
Telangiectasia			
subjects affected / exposed	5 / 160 (3.13%)		
occurrences (all)	5		
Infections and infestations			
COVID-19			
subjects affected / exposed	19 / 160 (11.88%)		
occurrences (all)	19		
Nasopharyngitis			
subjects affected / exposed	9 / 160 (5.63%)		
occurrences (all)	10		
Urinary tract infection			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	5 / 160 (3.13%)		
occurrences (all)	5		
Iron deficiency			
subjects affected / exposed	7 / 160 (4.38%)		
occurrences (all)	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