Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Group-sequential, Adaptive, Phase 3 Study With Open-label Extension Period to Assess the Efficacy and Safety of Selexipag as an add-on to Standard of Care Therapy in Subjects With Inoperable or Persistent/Recurrent After Surgical and/or Interventional Treatment Chronic Thromboembolic Pulmonary Hypertension

Summary

EudraCT number	2018-002823-41
Trial protocol	DE GB CZ BE NL HU AT BG DK PT IT
Global end of trial date	07 June 2022

Results information

Result version number	v1 (current)
This version publication date	16 June 2023
First version publication date	16 June 2023

Trial information

Trial identification

Sponsor protocol code	AC-065B302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03689244
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.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	07 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the effect of selexipag on pulmonary vascular resistance (PVR) versus placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (that is, technically non-operable) and persistent/recurrent CTEPH after surgical pulmonary endarterectomy (PEA) and/or interventional balloon pulmonary angioplasty [BPA]) treatment at Week 20.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2019
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: 4
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	China: 2
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Poland: 4

Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	128
EEA total number of subjects	49

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)	60
From 65 to 84 years	67
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 321 subjects were screened, of which 128 were randomly assigned and received study intervention.

Period 1

Period 1 title	Double Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Period: Placebo

Arm description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with single dose of placebo matching to selexipag 200 mcg tablet orally in the evening of day 1 and continued the same dose BID on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg placebo until reaching the individual iMTD in the range of 200 to 1600 mcg placebo BID or QD.

Arm title	Double-blind Period: Selexipag

Arm description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD.

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	JNJ-67896049
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with single dose of selexipag 200 mcg tablet orally in the evening of day 1 and continued the same dose BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching the individual iMTD in the range of 200 to 1600 mcg BID or QD.

Number of subjects in period 1	Double-blind Period: Placebo	Double-blind Period: Selexipag
Started	64	64
Completed	9	6
Not completed	55	58
Consent withdrawn by subject	7	8
Physician decision	2	2
Death	1	-
Unspecified	1	1
Sponsor decision	44	47

Period 2

Period 2 title	Open Label Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open Label Period: Selexipag (Ex-Placebo)

Arm description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months).

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	JNJ-67896049
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single tablet of selexipag 200 mcg orally BID. For subjects with Child-Pugh B or who had taken concomitantly a moderate CYP2C8 inhibitor, the dosing frequency was QD.

Arm title	Open Label Period: Selexipag (Ex-Selexipag)

Arm description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months).

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	JNJ-67896049
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single tablet of selexipag 200 mcg orally BID. For subjects with Child-Pugh B or who had taken concomitantly a moderate CYP2C8 inhibitor, the dosing frequency was QD.

Number of subjects in period 2	Open Label Period: Selexipag (Ex-Placebo)	Open Label Period: Selexipag (Ex-Selexipag)
Started	9	6
Completed	0	0
Not completed	9	6
Consent withdrawn by subject	1	-
Physician decision	1	-
Sponsor decision	7	6

Baseline characteristics

Reporting groups

Reporting group title	Double-blind Period: Placebo

Reporting group description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD).

Reporting group title	Double-blind Period: Selexipag

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD.

Reporting group values	Double-blind Period: Placebo	Double-blind Period: Selexipag	Total
Number of subjects	64	64	128
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	36	60
From 65 to 84 years	39	28	67
85 years and over	1	0	1
Title for AgeContinuous Units: years			
arithmetic mean	64	62	
standard deviation	± 13.22	± 14.38	-
Title for Gender Units: subjects			
Female	47	46	93
Male	17	18	35

End points

End points reporting groups

Reporting group title	Double-blind Period: Placebo

Reporting group description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) twice daily (BID) on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the individual maximum tolerated dose (iMTD) in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be once daily (QD).

Reporting group title	Double-blind Period: Selexipag

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was to be QD.

Reporting group title	Open Label Period: Selexipag (Ex-Placebo)

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months).

Reporting group title	Open Label Period: Selexipag (Ex-Selexipag)

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months).

Primary: Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 20

End point title	Change From Baseline in Pulmonary Vascular Resistance (PVR) at Week 20

End point description:

Change from baseline in PVR at Week 20 was reported. PVR was assessed by right or right and left heart catheterization. Change from Baseline was measured as ratio of post-dose visit value to baseline value. Hemodynamic set (HES) included all assigned subjects in the hemodynamic cohort. Here, "Measure type (Least Squares Mean)" indicated "Geometric LS mean".

End point type	Primary

End point timeframe:

Baseline (Day 1, pre-dose), within 2 to 5 hours post-dose on Week 20

End point values	Double-blind Period: Placebo	Double-blind Period: Selexipag		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: Ratio				
least squares mean (confidence interval 95%)	89.52 (81.78 to 97.99)	85.15 (77.97 to 92.99)		

Statistical analyses

Statistical analysis title	Selexipag Versus Placebo
Statistical analysis description: Ratio of Geometric mean of Selexipag to Placebo was reported.	
Comparison groups	Double-blind Period: Placebo v Double-blind Period: Selexipag
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412
Method	ANCOVA
Parameter estimate	Ratio of geometric LS mean
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.07

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For DB period: from first DB dose up to EDBT (that is, up to 27.7 months) and for OL extension period: from first OL dose up to 30 days after the last OL dose (that is, up to 21.8 months)

Adverse event reporting additional description:

Safety Analysis Set (SAF) included all subjects who received at least one dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Double-blind Period: Placebo

Reporting group description:

Subjects received a single oral tablet of placebo matching to selexipag 200 micrograms (mcg) in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, placebo dose was up titrated with weekly increments of 200 mcg until reaching the iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to end of DB treatment period (EDBT), further up-titration was done but not above 1600 mcg, BID (maximum duration: 24.6 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was QD.

Reporting group title	Open Label Period: Selexipag (Ex-Selexipag)

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 19.8 months).

Reporting group title	Open Label Period: Selexipag (Ex-Placebo)

Reporting group description:

All subjects who completed DB treatment period, entered OL extension period, and received the first dose (selexipag 200 mcg) of OL period in the evening of the EDBT and then 200 mcg BID on the day after. Subjects with moderate hepatic impairment (Child-Pugh B) or who had taken concomitantly moderate CYP2C8 inhibitor(s) started one tablet of OL selexipag 200 mcg in the morning of the day after EDBT visit. Dose up-titration was done as like DB treatment till iMTD was reached. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 20.8 months).

Reporting group title	Double-blind Period: Selexipag

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg in the evening of Day 1 and continued the same dose (200 mcg) BID on Day 2. Upon first dose toleration, selexipag dose was up titrated with weekly increments of 200 mcg until reaching iMTD in the range of 200 to 1600 mcg BID. The up titration up to Week 12 was followed by a stable maintenance treatment period with the iMTD (reached at Week 12) until Week 26. After Week 26 up to EDBT, further up-titration was done but not above 1600 mcg, BID (maximum duration: 27.7 months). For subjects with moderate hepatic impairment (Child-Pugh B) or who were concomitantly taking a moderate CYP2C8 inhibitor, the dosing frequency was QD.

Serious adverse events	Double-blind Period: Placebo	Open Label Period: Selexipag (Ex-Selexipag)	Open Label Period: Selexipag (Ex-Placebo)
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 64 (25.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Cancer			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular Tachycardia			

subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right Ventricular Failure			
subjects affected / exposed	3 / 64 (4.69%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Second Degree			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter Site Haematoma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Gastrointestinal disorders			
Discoloured Vomit			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis Acute			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	2 / 64 (3.13%)	0 / 6 (0.00%)	0 / 9 (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
Haemoptysis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			

subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 64 (3.13%)	0 / 6 (0.00%)	0 / 9 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (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
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-blind Period: Selexipag		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 64 (14.06%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urethral Cancer			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate Cancer			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower Limb Fracture			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural Haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Atrioventricular Block Second Degree			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Atrial Flutter			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheter Site Haematoma			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Discoloured Vomit			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis Acute			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Acute Respiratory Failure				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Hypertension				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute Kidney Injury				
subjects affected / exposed	1 / 64 (1.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Bronchitis			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Covid-19 Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia Bacterial			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral Infection			

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-blind Period: Placebo	Open Label Period: Selexipag (Ex-Selexipag)	Open Label Period: Selexipag (Ex-Placebo)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 64 (70.31%)	5 / 6 (83.33%)	9 / 9 (100.00%)
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
Hot Flush			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	2 / 64 (3.13%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	2	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Palpitations			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	7 / 64 (10.94%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	8	0	2
Headache			
subjects affected / exposed	14 / 64 (21.88%)	2 / 6 (33.33%)	6 / 9 (66.67%)
occurrences (all)	24	2	11
Hypoaesthesia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	4	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Chest Pain			
subjects affected / exposed	3 / 64 (4.69%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	1
Fatigue			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0
Oedema			
subjects affected / exposed	3 / 64 (4.69%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	1
Oedema Peripheral			
subjects affected / exposed	8 / 64 (12.50%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	11	0	0
Pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Irritable Bowel Syndrome			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	4 / 64 (6.25%)	1 / 6 (16.67%)	3 / 9 (33.33%)
occurrences (all)	5	1	5
Vomiting			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	3 / 9 (33.33%)
occurrences (all)	1	1	4
Diarrhoea			
subjects affected / exposed	9 / 64 (14.06%)	1 / 6 (16.67%)	5 / 9 (55.56%)
occurrences (all)	11	2	8
Abdominal Pain Upper			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Abdominal Distension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Abdominal Discomfort			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 64 (14.06%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	10	0	0
Pulmonary Hypertension			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 64 (6.25%)	1 / 6 (16.67%)	3 / 9 (33.33%)
occurrences (all)	6	1	4

Back Pain			
subjects affected / exposed	5 / 64 (7.81%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	6	0	1
Flank Pain			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Muscle Spasms			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	5 / 64 (7.81%)	0 / 6 (0.00%)	4 / 9 (44.44%)
occurrences (all)	5	0	6
Pain in Extremity			
subjects affected / exposed	4 / 64 (6.25%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	4	1	1
Pain in Jaw			
subjects affected / exposed	2 / 64 (3.13%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	2	0	2
Infections and infestations			
Covid-19			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	4	0	2
Gastroenteritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Decreased Appetite			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Steroid Diabetes			

subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vitamin D Deficiency			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Double-blind Period: Selexipag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 64 (93.75%)		
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	6		
Hot Flush			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	2		
Flushing			
subjects affected / exposed	4 / 64 (6.25%)		
occurrences (all)	5		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	10		
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 64 (12.50%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	36 / 64 (56.25%)		
occurrences (all)	65		

Hypoaesthesia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences (all)	3		
Anaemia			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 64 (4.69%)		
occurrences (all)	4		
Chest Pain			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	6 / 64 (9.38%)		
occurrences (all)	11		
Oedema			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences (all)	0		
Oedema Peripheral			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	6		
Gastrointestinal disorders			
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	17 / 64 (26.56%)		
occurrences (all)	29		

Vomiting subjects affected / exposed occurrences (all)	11 / 64 (17.19%) 14		
Diarrhoea subjects affected / exposed occurrences (all)	38 / 64 (59.38%) 57		
Abdominal Pain Upper subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5		
Abdominal Distension subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4		
Abdominal Discomfort subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3		
Pulmonary Hypertension subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Erythema subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 3		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	14 / 64 (21.88%) 16		
Back Pain subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5		
Flank Pain subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		

Muscle Spasms subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 3		
Myalgia subjects affected / exposed occurrences (all)	7 / 64 (10.94%) 7		
Pain in Extremity subjects affected / exposed occurrences (all)	13 / 64 (20.31%) 16		
Pain in Jaw subjects affected / exposed occurrences (all)	16 / 64 (25.00%) 20		
Infections and infestations Covid-19 subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1		
Pneumonia subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Decreased Appetite subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 6		
Steroid Diabetes subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Vitamin D Deficiency subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2019	• Several inclusion criteria were revised with the aim of ensuring the recruitment of subjects who could potentially benefit from medical therapy (only technically non operable participants assessed based on imaging review for all CTEPH subpopulations) and who had substantially impaired pulmonary vascular function (PVR greater than or equal to [>=]400 dynes.second/centimeter^5 or >=5 Wood units). • Statistical changes were made following interactions with health authorities.
16 April 2020	• The study design was revised to power the study for the additional clinical endpoint, time to clinical worsening (TTCW). As a result, elements of the study design, key secondary endpoints, sample size, testing hierarchy and analysis timepoints were amended to ensure the evaluation of 6-minute walk distance (6MWD) and TTCW endpoints. • The DB period was changed from a fixed duration of 52 weeks to a variable duration (maximum 52 months) based on the timepoint at which the overall target number of TTCW events would be reached (or earlier following the recommendation of the independent data monitoring committee (IDMC) or sponsor's decision). • The stratification factor of CTEPH population was redefined to inoperable (with or without BPA) versus persistent/recurrent after PEA (including PEA followed by BPA). • For the non-hemodynamic cohort, the PVR threshold for inclusion was changed to >=300 dyn.sec/cm^5 or >=3.75 Wood units. • The sponsor's standardised guidelines for the assessments heart catheterisation (HC), 6MWT and Borg dyspnea index (BDI) were added to the protocol and the Borg CR10 Scale®was added. • A clinical event committee (CEC) was set up in order to ensure independent adjudication of clinical worsening events.
29 September 2020	• Statistical changes were made in line with the resolution of food and drug administration (FDA) queries. • The maximum duration of the DB period was increased from 52 months to 59 months. • Safety reporting requirements were updated in line with Janssen processes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Failure to meet success on the primary endpoint led to termination of the study for futility and thus the pre-planned testing hierarchy was no longer applicable, and all efficacy analyses other than the primary endpoint (PVR) were exploratory.

Notes: