Clinical trial results:
A Prospective, Multicenter, Single-arm, Open-label, Phase 4 Study of the Effects of Selexipag on Right Ventricular Remodeling in Pulmonary Arterial Hypertension Assessed by Cardiac Magnetic Resonance Imaging (RESTORE)

Summary

EudraCT number	2019-004783-22
Trial protocol	NL DE GB FR
Global end of trial date	28 July 2023

Results information

Result version number	v1 (current)
This version publication date	02 August 2024
First version publication date	02 August 2024

Trial information

Trial identification

Sponsor protocol code	67896049PAH4005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04435782
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium,
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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	13 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to assess the effects of selexipag on right ventricle (RV) function in subjects with pulmonary arterial hypertension (PAH).

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 Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Singapore: 1
Worldwide total number of subjects	9
EEA total number of subjects	1

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)	9

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 25 subjects were screened, out of which 9 subjects were enrolled and were treated with selexipag.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Selexipag

Arm description:

Subjects with PAH received a 200 micrograms (mcg) selexipag tablet orally on the evening of Day 1, followed by twice-daily dosing starting from Day 2. The dose of selexipag was increased by 200 mcg each week to allow each subject to reach their individual maximum dose (iMD), up to 1600 mcg twice daily, by the end of Week 12. From Week 13 onwards, subjects received their iMD of 1600 mcg selexipag tablets orally twice daily until Week 52. Subjects were then followed for safety up to 30 days after the last dose of selexipag.

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	ACT-293987, JNJ-67896049
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received selexipag 200 mcg tablet orally on Day 1 in the evening then twice daily starting from Day 2. Dose of selexipag was up-titrated every week by 200 mcg to allow each subject to reach their iMD to 1,600 mcg twice daily orally by end of Week 12. Starting from Week 13, subjects received iMD of selexipag 1600 mcg tablet orally twice daily up to Week 52.

Number of subjects in period 1	Selexipag
Started	9
Completed	5
Not completed	4
Study terminated by sponsor	4

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
Subjects with PAH received a 200 micrograms (mcg) selexipag tablet orally on the evening of Day 1, followed by twice-daily dosing starting from Day 2. The dose of selexipag was increased by 200 mcg each week to allow each subject to reach their individual maximum dose (iMD), up to 1600 mcg twice daily, by the end of Week 12. From Week 13 onwards, subjects received their iMD of 1600 mcg selexipag tablets orally twice daily until Week 52. Subjects were then followed for safety up to 30 days after the last dose of selexipag.	

Reporting group values	Selexipag	Total	
Number of subjects	9	9	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42.2		
standard deviation	± 13.28	-	
Gender Categorical Units: Subjects			
Female	6	6	
Male	3	3	

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects with PAH received a 200 micrograms (mcg) selexipag tablet orally on the evening of Day 1, followed by twice-daily dosing starting from Day 2. The dose of selexipag was increased by 200 mcg each week to allow each subject to reach their individual maximum dose (iMD), up to 1600 mcg twice daily, by the end of Week 12. From Week 13 onwards, subjects received their iMD of 1600 mcg selexipag tablets orally twice daily until Week 52. Subjects were then followed for safety up to 30 days after the last dose of selexipag.

Primary: Change from Baseline to Week 26 in Right Ventricular Stroke Volume (RVSV) Assessed by Pulmonary Artery Flow Magnetic Resonance Imaging (MRI)

End point title	Change from Baseline to Week 26 in Right Ventricular Stroke Volume (RVSV) Assessed by Pulmonary Artery Flow Magnetic Resonance Imaging (MRI)[1]

End point description:

Change from baseline to Week 26 in RVSV assessed by pulmonary artery flow MRI was reported. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the statistical analysis plan (SAP), subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Primary

End point timeframe:

Baseline, Week 26

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Millilitre (mL)				
number (not applicable)				
Subject 1 (n =1)	38.35			
Subject 2 (n =1)	-1.53			
Subject 3 (n =1)	16.53			
Subject 4 (n =1)	11			
Subject 5 (n =1)	27.2			
Subject 6 (n =1)	14.07			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Right Ventricular End-Diastolic Volume (RVEDV) Assessed by MRI

End point title	Change from Baseline to Week 26 in Right Ventricular End-Diastolic Volume (RVEDV) Assessed by MRI

End point description:

Change from baseline to Week 26 in RVEDV assessed by MRI was reported. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: millilitre				
number (not applicable)				
Subject 1 (n =1)	40.57			
Subject 2 (n =1)	-8.89			
Subject 3 (n =1)	23.58			
Subject 4 (n =1)	6.79			
Subject 5 (n =1)	3.71			
Subject 6 (n =1)	7.82			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Right Ventricular End-Systolic Volume (RVESV) Assessed by MRI

End point title	Change from Baseline to Week 26 in Right Ventricular End-Systolic Volume (RVESV) Assessed by MRI

End point description:

Change from baseline to Week 26 in right ventricular end-systolic volume (RVESV) assessed by MRI was reported. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Millilitre				
number (not applicable)				
Subject 1 (n =1)	2.23			
Subject 2 (n =1)	-7.36			
Subject 3 (n =1)	7.05			
Subject 4 (n =1)	-4.22			
Subject 5 (n =1)	-23.5			
Subject 6 (n =1)	-6.25			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Right Ventricular Ejection Fraction (RVEF) Assessed by MRI

End point title	Change from Baseline to Week 26 in Right Ventricular Ejection Fraction (RVEF) Assessed by MRI

End point description:

Change from baseline to Week 26 in right ventricular ejection fraction (RVEF) assessed by MRI was reported. Right ventricular ejection fraction (RVEF) was the fraction of the end-diastolic volume (EDV) that is ejected out of right ventricle with each contraction. EDV is the volume of blood within a ventricle immediately before a contraction. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage of EDV				
number (not applicable)				
Subject 1 (n =1)	9.65			
Subject 2 (n =1)	0.42			
Subject 3 (n =1)	6.96			
Subject 4 (n =1)	5.01			
Subject 5 (n =1)	19.12			
Subject 6 (n =1)	7.62			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Right Ventricular (RV) Mass Index Assessed by MRI

End point title	Change from Baseline to Week 26 in Right Ventricular (RV) Mass Index Assessed by MRI

End point description:

Change from baseline to Week 26 in RV mass index assessed by MRI was reported. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Grams per meter square (g/m^2)				
number (not applicable)				
Subject 1 (n =1)	-11.03			
Subject 2 (n =1)	2.72			
Subject 3 (n =1)	-12.69			
Subject 4 (n =1)	0.09			
Subject 5 (n =1)	-16.56			
Subject 6 (n =1)	-2.41			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in RIght Ventricular Global Longitudinal Strain (RVGLS) Assessed by MRI

End point title	Change from Baseline to Week 26 in RIght Ventricular Global Longitudinal Strain (RVGLS) Assessed by MRI

End point description:

Change in RVGLS was a measure of longitudinal percent change in length of endocardium at Week 26 from baseline length assessed by MRI. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percent change in length of endocardium				
number (not applicable)				
Subject 1: RVGLS Endocardium (n =1)	-4.26			
Subject 2: RVGLS Endocardium (n =1)	-5.31			
Subject 3: RVGLS Endocardium (n =1)	-12.8			
Subject 4: RVGLS Endocardium (n =1)	-5.61			
Subject 5: RVGLS Endocardium (n =1)	-14.45			
Subject 6: RVGLS Endocardium (n =1)	-1.74			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change from Baseline to Week 26 in World Health Organization (WHO) Functional Class

End point title	Number of Subjects With Change from Baseline to Week 26 in World Health Organization (WHO) Functional Class

End point description:

WHO functional classification for PAH ranged from Class I (no limitation in physical activity, ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope), Class II (slight limitation of physical activity, ordinary physical activity cause undue dyspnea or fatigue, chest pain or near syncope), Class III (marked limitation of physical activity, less than ordinary activity cause undue dyspnea or fatigue, chest pain or near syncope) & Class IV (cannot perform a physical activity without any symptoms, dyspnea and/or fatigue may even be present at rest). Change from baseline in WHO functional class was classified into "Improved", "No change" and "Worsened". Improvement =reduction in functional class; worsened =increase in functional class; and no change = no change in functional class. Safety set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Subjects				
Baseline: Class I	0			
Baseline: Class II	4			
Baseline: Class III	4			
Baseline: Class IV	0			
Week 26: Improved	3			
Week 26: Unchanged	5			
Week 26: Worsened	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in N-terminal-Pro-Hormone Brain Natriuretic Peptide (NT-proBNP)

End point title	Change from Baseline to Week 26 in N-terminal-Pro-Hormone Brain Natriuretic Peptide (NT-proBNP)

End point description:

NT pro-BNP is a cardiac biomarker that is released in the blood in response to changes in the pressure inside of the heart. Levels go up when heart failure develops or gets worse, and levels go down when heart failure is stable or improves. This biomarker helps to measure the changes in the severity of heart failure over time in response to therapy. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanograms/litre (ng/L)				
number (not applicable)				
Subject 1 (n =1)	-202.376			
Subject 2 (n =1)	142.9233			
Subject 3 (n =1)	-261.4904			
Subject 4 (n =1)	78.6501			
Subject 5 (n =1)	-215.8226			
Subject 6 (n =1)	-762.5677			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in 6-Minute Walk Distance (6MWD)

End point title	Change from Baseline to Week 26 in 6-Minute Walk Distance (6MWD)

End point description:

6MWD was the distance that a subjects could walk in 6 minutes. Subjects were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Safety analysis set

included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Metre				
number (not applicable)				
Subject 1 (n =1)	-72			
Subject 2 (n =1)	0			
Subject 3 (n =1)	275			
Subject 4 (n =1)	14			
Subject 5 (n =1)	17			
Subject 6 (n =1)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Marked Laboratory Abnormalities

End point title	Number of Subjects With Treatment-Emergent Marked Laboratory Abnormalities

End point description:

Number of subjects with treatment-emergent marked laboratory abnormalities in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, creatinine, sodium, potassium, hemoglobin, hematocrit; EVF; PCV (male), hematocrit; EVF; PCV (female), platelets (assuming no platelet cluster), leukocytes; white blood cells, Neutrophils (Abs), Eosinophils (Abs), lymphocytes (Abs) were reported. Abnormalities that occurred after study treatment start and up to last dose, that were not present at baseline, were treatment-emergent. Treatment-emergent marked laboratory abnormalities were determined at the investigator's discretion. Safety analysis set included all subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Day 1 up to 3 days after last dose of study drug (up to 52 weeks and 3 days that is 367 days)

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE) was any untoward medical occurrence that at any dose resulted in death, was life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a suspected transmission of any infectious agent via a medicinal product. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 3 days was considered as treatment emergent. Safety analysis set included all subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Day 1 up to 3 days after last dose of study drug (up to 52 weeks and 3 days that is 367 days)

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
AEs	9			
SAEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) Leading to Premature Discontinuation of Study Drug

End point title	Number of Subjects With Adverse Events (AEs) Leading to Premature Discontinuation of Study Drug

End point description:

Number of subjects with AEs leading to premature discontinuation of study drug were reported. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Safety analysis set included all subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Day 1 up to last dose of study drug (up to Week 52)

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events Adverse Events of Special Interest (AESI)

End point title	Number of Subjects With Adverse Events Adverse Events of Special Interest (AESI)

End point description:

Number of subjects with AESI were reported. An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. AESI were anaemia, bleeding events, gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction), hyperthyroidism, hypotension, light-dependent non-melanoma skin malignancies, major adverse cardiovascular events (MACE), medication errors, ophthalmological effects associated to retinal vascular system, pregnancy, pulmonary venoocclusive disease associated with pulmonary oedema, renal function impairment / acute renal failure. Safety analysis set included all subjects who received at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Day 1 up to 3 days after last dose of study drug (up to 52 weeks and 3 days that is 367 days)

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Number of Non-invasive Low-risk Criteria Among the 8 Variables

End point title	Change from Baseline to Week 26 in Number of Non-invasive Low-risk Criteria Among the 8 Variables

End point description:

Risk score is derived for each subject considering following non-invasive low-risk criteria among 8 variables: absence of clinical signs of right heart failure, absence of symptoms progression, absence of syncope, WHO FC I-II, 6MWD >440 meter, NT-proBNP <300 ng/L, Right atrial (RA) area <18 centimeter square (cm^2) as determined by echocardiography (Echo), absence of pericardial effusion, as determined by Echo. Number of low-risk criteria at baseline & Week 26 constitutes risk score & were derived for each subject by adding '1' for each of above criteria met. Number of low-risk criteria among 8 variables for each subject can vary from 0 (worse subjects) to 8 (healthier subjects). Higher score indicated healthier subjects. Safety set. Here, N (number of subjects analysed) =subjects evaluable for this endpoint & "n" signifies subjects evaluable for specified rows. As pre-specified in SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Score on a scale				
number (not applicable)				
Subject 1 (n =1)	1			
Subject 2 (n =1)	1			
Subject 3 (n =1)	3			
Subject 4 (n =1)	1			
Subject 5 (n =1)	1			
Subject 6 (n =1)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Number of Non-invasive Low-risk Criteria Among the 3 Variables

End point title	Change from Baseline to Week 26 in Number of Non-invasive Low-risk Criteria Among the 3 Variables

End point description:

The risk score is derived for each subject considering the following non-invasive low-risk criteria among the 3 variables: WHO FC I-II, 6MWD >440 m, NT-proBNP < 300 ng/L. Number of low-risk criteria at baseline and Week 26 constitutes risk score and were derived for each subject by adding '1' for each of above criteria met. Number of low-risk criteria among the 3 variables for each subject can vary from 0 (worse subjects) to 3 (healthier subjects). Higher score indicated healthier subjects. Safety analysis set included all subjects who received at least 1 dose of study intervention. Here, N (number of subjects analysed) signifies subjects evaluable for this endpoint and "n" signifies subjects evaluable for specified rows. As pre-specified in the SAP, subject wise data was collected and reported due to very limited number of subjects enrolled.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Score on a scale				
number (not applicable)				
Subject 1 (n =1)	1			
Subject 2 (n =1)	0			
Subject 3 (n =1)	2			
Subject 4 (n =1)	1			
Subject 5 (n =1)	1			
Subject 6 (n =1)	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Cause Mortality: Day 1 up to 30 days after last dose of drug (up to Week 56), SAEs and non-SAEs: Day 1 up to 3 days after last dose of study drug (up to 52 weeks and 3 days that is 367 days)

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of study intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects with PAH received a 200 micrograms (mcg) selexipag tablet orally on the evening of Day 1, followed by twice-daily dosing starting from Day 2. The dose of selexipag was increased by 200 mcg each week to allow each subject to reach their individual maximum dose (iMD), up to 1600 mcg twice daily, by the end of Week 12. From Week 13 onwards, subjects received their iMD of 1600 mcg selexipag tablets orally twice daily until Week 52. Subjects were then followed for safety up to 30 days after the last dose of selexipag.

Serious adverse events	Selexipag		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal Haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)		
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	Selexipag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hot Flush			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Face Oedema			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Chest Pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oedema Peripheral			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspnoea Exertional			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Investigations			
Weight Decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Body Temperature Increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vitamin D Decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness Exertional			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	7		
Hypoaesthesia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Eye disorders Xerophthalmia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dental Caries subjects affected / exposed occurrences (all) Abdominal Discomfort subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 5 / 9 (55.56%) 8 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 2 2 / 9 (22.22%) 3 7 / 9 (77.78%) 8		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2		

Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Renal Pain subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2 1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Joint Swelling subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in Jaw subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 5 / 9 (55.56%) 6 4 / 9 (44.44%) 4		
Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Fungal Skin Infection subjects affected / exposed occurrences (all) Covid-19 subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 2 3 / 9 (33.33%) 3		
Metabolism and nutrition disorders Iron Deficiency			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Decreased Appetite			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2021	The overall reason for this protocol amendment was to provide clarification for several inclusion and exclusion criteria to better define the target population that may benefit from the study intervention, to add exploratory objectives and endpoints for long-term outcomes, to adapt to changed internal safety language and reporting processes, to align with TransCelerate template and to implement minor corrections and editorial revisions.
25 March 2022	Overall reasons for this protocol amendment was to clarify selected inclusion and exclusion criteria to better define the target population that might benefit from the study intervention and to clarify the definition of end of study (EOS) for the subjects continuing selexipag treatment in a continued access program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported