Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled Study in Participants With Sarcoidosis-associated Pulmonary Hypertension (SAPH) to Assess the Efficacy and Safety of Oral Selexipag

Summary

EudraCT number	2018-004887-74
Trial protocol	GB NL DE HU PL ES BE IT
Global end of trial date	19 April 2023

Results information

Result version number	v1 (current)
This version publication date	26 April 2024
First version publication date	26 April 2024

Trial information

Trial identification

Sponsor protocol code	AC-065D301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03942211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
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	11 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the effect of selexipag compared to placebo on pulmonary artery pressure (PVR) in subjects with sarcoidosis-associated pulmonary hypertension (SAPH) up to Week 26.

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	26 February 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	Spain: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	10
EEA total number of subjects	7

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)	4
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 10 subjects were enrolled and treated, none of them completed the study.

Period 1

Period 1 title	Overall Study (overall 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	Selexipag

Arm description:

Subjects received a single oral tablet of selexipag 200 mcg on Day 1. The dose was up-titrated by the investigator/delegate at weekly intervals to allow each subject to reach their individual maximum tolerated dose (iMTD), in the range of 200 mcg to 1600 mcg (that is, 1 to 8 tablets) twice daily from Day 2 to Week 12 or until reaching iMTD. From Week 12 onwards, subjects received their iMTD of selexipag orally twice daily until end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.

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

Dosage and administration details:

Subjects received a single dose of selexipag 200 mcg on Day 1. The dose was up-titrated by the investigator/delegate at weekly intervals to allow each subjects to reach their individual iMTD, in the range of 200 mcg to 1600 mcg (that is, 1 to 8 tablets) twice daily from Day 2 to Week 12 or until reaching iMTD. From Week 12 onwards, subjects received their iMTD of selexipag orally twice daily till end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.

Arm title	Placebo

Arm description:

Subjects received placebo matching to selexipag 1 to 8 tablets twice daily from Day 1 till end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.

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 received placebo matching to selexipag from Day 1 till end of treatment (up to 456 days).

Number of subjects in period 1	Selexipag	Placebo
Started	6	4
Completed	0	0
Not completed	6	4
Adverse event, serious fatal	1	-
Adverse event, non-fatal	-	1
Study terminated by sponsor	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
Subjects received a single oral tablet of selexipag 200 mcg on Day 1. The dose was up-titrated by the investigator/delegate at weekly intervals to allow each subject to reach their individual maximum tolerated dose (iMTD), in the range of 200 mcg to 1600 mcg (that is, 1 to 8 tablets) twice daily from Day 2 to Week 12 or until reaching iMTD. From Week 12 onwards, subjects received their iMTD of selexipag orally twice daily until end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matching to selexipag 1 to 8 tablets twice daily from Day 1 till end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.	

Reporting group values	Selexipag	Placebo	Total
Number of subjects	6	4	10
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	0	4
From 65 to 84 years	2	4	6
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	55	68.5	
standard deviation	± 14.53	± 2.38	-
Title for Gender Units: subjects			
Female	2	2	4
Male	4	2	6

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

Subjects received a single oral tablet of selexipag 200 mcg on Day 1. The dose was up-titrated by the investigator/delegate at weekly intervals to allow each subject to reach their individual maximum tolerated dose (iMTD), in the range of 200 mcg to 1600 mcg (that is, 1 to 8 tablets) twice daily from Day 2 to Week 12 or until reaching iMTD. From Week 12 onwards, subjects received their iMTD of selexipag orally twice daily until end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matching to selexipag 1 to 8 tablets twice daily from Day 1 till end of treatment (up to 456 days). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking moderate CYP2C8 inhibitor(s) the dosing frequency was once daily.

Primary: Pulmonary Vascular Resistance (PVR) up to Week 26

End point title	Pulmonary Vascular Resistance (PVR) up to Week 26[1]

End point description:

PVR represents the resistance against which the right ventricle needs to pump and determined by right heart catheterization (RHC). It was measured as the ratio of the PVR value post-treatment initiation up to Week 26 (post) versus the PVR value pre-treatment initiation at baseline (pre), expressed as a percentage of baseline value. The baseline reference value for PVR was based on the last RHC performed prior to study intervention initiation. As specified in the statistical analysis plan, data was not planned to be summarised for this endpoint and only individual subject wise data was collected. Randomised analysis set: subjects assigned to the study intervention. 'N' (number of subjects analyzed): subjects evaluable for this endpoint; 'n' (number analysed): number of subjects randomised and analysed in respective treatment arm. Here, 99999 signifies PVR data was not reported as no subject was randomised in that treatment arm.

End point type	Primary

End point timeframe:

Baseline up to 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: Descriptive statistics was done, no inferential statistical analysis was performed.

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: percentage of baseline PVR				
number (not applicable)				
Subject 1 (n=0,1)	99999	89.0		
Subject 2 (n=0,1)	99999	201		
Subject 3 (n=0,1)	99999	56		
Subject 4 (n=1,0)	88	99999		
Subject 5 (n=1,0)	100	99999		
Subject 6 (n=1,0)	47.0	99999		
Subject 7 (n=1,0)	82.0	99999		
Subject 8 (n=1,0)	86.0	99999		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 456 days

Adverse event reporting additional description:

Safety assessments were based on the safety analysis set which included all participants who received at least one 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 were up-titrated and received Selexipag in the range of 200 micrograms (mcg) to 1600 mcg (that is, 1 to 8 tablets) once or twice from daily Day 1 till Week 26 to allow each subject to reach their individual maximum tolerated dose (iMTD). For subjects with moderate hepatic impairment (Child-Pugh Class B) or who were concomitantly taking a moderate cytochrome P450 (CYP)2C8 inhibitor(s) received Selexipag once daily.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matching to selexipag 1 to 8 tablets twice daily from Day 1 till Week 26. Subjects with moderate hepatic impairment (Child-Pugh Class B) or who concomitantly received moderate cytochrome P450 (CYP)2C8 inhibitor(s) received Selexipag matching placebo once daily from Day 1 till Week 26.

Serious adverse events	Selexipag	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	3 / 4 (75.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Selexipag	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 4 (75.00%)	
Vascular disorders			
Flushing			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Cyanosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oedema Peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Investigations			
Platelet Count Decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Neutrophil Count Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
N-Terminal Prohormone Brain Natriuretic Peptide Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

Mean Cell Volume Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Mean Cell Haemoglobin Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Lymphocyte Count Decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Glycosylated Haemoglobin Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Red Blood Cell Count Decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Injection Related Reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 6 (83.33%)	1 / 4 (25.00%)	
occurrences (all)	11	2	
Migraine			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	1 / 4 (25.00%)	
occurrences (all)	13	1	
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Papulopustular Rosacea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Pain in Jaw			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Limb Discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Back Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pain in Extremity			
subjects affected / exposed	4 / 6 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	4 / 6 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Sputum Purulent			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Covid-19			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Conjunctivitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Vitamin B12 Deficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vitamin D Deficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2019	The purpose of the amendment was to to revise the study design following Health Authority (HA) feedback that recommended that the study should also be powered for clinical endpoints such as time to clinical worsening, 6-minute walk distance (6MWD) and patient reported outcomes (PRO).
21 September 2020	The purpose of the amendment was to clarify the Child-Pugh assessments, add a Coronavirus Disease 2019 (COVID-19) appendix, adapt internal safety reporting processes, align with TransCelerate template, make minor corrections, and perform editorial document formatting revisions.
25 February 2022	The purpose of the amendment was to modify some inclusion and exclusion criteria aiming to facilitate enrollment (based on inputs from the Steering Committee [SC] of the SPHINX study), update Coronavirus Disease 2019 (COVID-19) appendix with recent updates pertaining to study conduct related to COVID-19 vaccine deployment for non-COVID-19 clinical trials, and implement miscellaneous minor corrections and clarifications.

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.

All planned efficacy analyses could not be performed due to early termination of study.

Notes: