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.

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The aim of the present study is to investigate whether selexipag could be helpful to treat patients with another form of PH called sarcoidosis-associated pulmonary hypertension (SAPH).

Ethical review	Approved WMO
Status	Completed
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON52661

Source
ToetsingOnline

Brief title
Effectiveness and safety study of selexipag in patients with SAPH

Condition

- Pulmonary vascular disorders

Synonym
High blood pressure in lung vessels associated with sarcoidosis, Sarcoidosis associated pulmonary hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Actelion Pharmaceuticals Ltd (in Nederland vertegenwoordigd door Janssen-Cilag B.V.)

Intervention

Keyword: Interventional clinical trial, Prostacyclin receptor agonist, Pulmonary hypertension, Sarcoidosis associated pulmonary hypertension

Outcome measures

Primary outcome

Pulmonary Vascular Resistance (PVR) on Study Intervention up to Week 26, 2-5h

post dose. PVR is measured by right heart

catheterization (RHC) and expressed as percent of baseline value.

Secondary outcome

No secondary outcome measures, rest of outcomes is exploratory.

Study description

Background summary

Pulmonary hypertension (PH) is a pathophysiological disorder that may involve multiple clinical conditions and can complicate several cardiovascular and respiratory diseases. Sarcoidosis is a multisystemic disorder that is characterized by non-caseating granulomas which are present in multiple tissues, particularly in the lung and lymphatic system. Severe untreated pulmonary hypertension (PH) carries a poor prognosis and is associated with higher mortality in participants with interstitial lung diseases and sarcoidosis. While there is no approved treatment for SAPH, PH-specific treatments are frequently used. Selexipag is a selective, orally available and long-acting non-prostanoid agonist of the prostacyclin receptor (prostacyclin [IP] receptor) for the treatment of patients with PAH. The rationale for this study is based on the unmet medical need for new therapeutic options for participants with SAPH and is supported by the established efficacy and safety of selexipag in the PAH indication, the shared pathomechanism between SAPH and PAH, and the available data on the efficacy and safety of

PH-specific therapies in SAPH.

Study objective

The aim of the present study is to investigate whether selexipag could be helpful to treat patients with another form of PH called sarcoidosis-associated pulmonary hypertension (SAPH).

Study design

This study consists of screening period, main observation period and double blind extension period and safety follow-up period. The duration of individual participation in the study will be different for each individual participant (between approximately 15 months and up to approximately 3.5 years) and will depend on the time of each participant*s individual date of entering the study and the total recruitment time. The efficacy assessments include right heart catheterization (RHC), assessment of exercise capacity, dyspnea, pulmonary function tests, etc. Safety and tolerability will be evaluated throughout the study and includes review of concomitant medications and adverse events (AEs), clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, physical examination, and pregnancy testing.

Intervention

Selexipag 200 micro gram (µg): Oral tablets containing 200 µg of selexipag. Depending on the iMTD, participants will receive 1 (200 µg) to 8 (1600 µg) tablets at each administration.

Study intervention will be up-titrated to allow each participant to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to1600 µg (ie, 1 to 8 tablets) bid/qd. Dosing frequency will be bid, except for participants with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking (a) moderate CYP2C8 inhibitor(s), who receive study intervention qd. The dose will be uptitrated by the investigator/delegate in 200 µg bid/qd increments at weekly intervals during scheduled TCs until reaching the iMTD. If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to 2 weeks. If needed, the dose can be reduced by 200 µg bid/qd.

Placebo: Oral tablets without active compound. Participants can receive 1 to 8 tablets at each administration.The comparator will be administered similarly to the experimental intervention.

Study burden and risks

Severe untreated pulmonary hypertension (PH) carries a poor prognosis and is associated with higher mortality in participants with interstitial lung diseases and sarcoidosis. While there is no approved treatment for SAPH, PH-specific treatments are frequently used. Selexipag is a selective, orally available and long-acting non-prostanoid agonist of the prostacyclin receptor (prostacyclin [IP] receptor) for the treatment of patients with PAH. The rationale for this study is based on the unmet medical need for new therapeutic options for participants with SAPH and is supported by the established efficacy and safety of selexipag in the PAH indication, the shared pathomechanism between SAPH and PAH, and the available data on the efficacy and safety of PH-specific therapies in SAPH.

Side effects of standard of care, side effects of selexipag, side effects of assessments and unknown risks may occur. Safety and tolerability will be evaluated throughout the study from signing of the informed consent form onwards until the last studyrelated activity (end of study/early withdrawal).

The dosage of selexipag will be up-titrated in 200 µg bid/qd increments at weekly intervals during scheduled TCs until reaching the iMTD. If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to 2 weeks. If needed, the dose can be reduced by 200 µg bid/qd. The decision to not further up-titrate the dose will be based on the investigator*s medical judgment based on the occurrence and severity of typical pharmacological effects of IP receptor agonists and the participant*s individual tolerability.

An IDMC will be established to monitor the safety of subjects and will review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in this study and to evaluate whether efficacy objectives are met. The IDMC will review the data and make recommendations to the sponsor Committee, which will be responsible for identifying appropriate actions based on the recommendations of the IDMC.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and other safety evaluations.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male or female
-18 to 75 years of age, inclusive
- Confirmed diagnosis of sarcoidosis as per ATS criteria
- Sarcoidosis-associated precapillary PH, confirmed by RHC (at rest) within 90 days prior to randomization.
- PH severity according to modified WHO FC II-IV at Screening and randomization; participants in WHO FC IV must be in a stable condition and able to perform a 6MWT.
- Either not receiving PH-specific treatment, or receiving PH-specific oral monotherapy (ie, riociguat or PDE5i or ERA); if on oral PH-specific monotherapy treatment has to be stable (ie, no introduction of new therapies or changes in dose) for at least 90 days prior to both the RHC qualifying for enrollment and randomization.
- Stable sarcoidosis treatment regimen, ie, no new specific anti inflammatory treatment for sarcoidosis for at least 90 days, and stable dose(s) for at least 30 days prior to both the RHC qualifying for enrollment and randomization.
- 6MWD between 50 and 450 m both at Screening and at the time of randomization.
- Forced vital capacity (FVC) >50% of predicted at Screening.

- FEV1/FVC >=60%, or if FEV1/FVC <60% then FEV1 must be >=60% of predicted at Screening.
- Women of childbearing potential must have a negative pregnancy test at screening and randomization, must agree to undertake monthly urine pregnancy tests, and to practice an acceptable method of contraception and agree to remain on an acceptable method while receiving study intervention and until 30 days after last dose of study intervention.
- A woman using oral contraceptives must have been using this method for at least 1 month prior to randomization.

Exclusion criteria

- PH due to left heart disease (PAWP >15 mmHg).
- History of left heart failure (LHF) as assessed by the investigator including cardiomyopathies and cardiac sarcoidosis, with a left ventricular ejection fraction (LVEF) <40%.
- Treatment with prostacyclin, prostacyclin analogues or IP receptor agonists (ie, selexipag) within 90 days prior to randomization and/or prior to the RHC qualifying for enrollment, except those given at vasodilator testing during RHC.
- SBP <90 mmHg at Screening or at randomization.
- Included on a lung transplant list or planned to be included until Visit 6 / Week 39.
- Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to RHC qualifying for enrollment.
- Received an investigational intervention or used an invasive investigational medical device within 90 days prior to randomization.
- Any condition for which, in the opinion of the investigator, participation would not be in the best interests of the participant (eg, compromise wellbeing), or that could prevent, limit, or confound the protocol-specified assessments.
- Any acute or chronic impairment that may influence the ability to comply with study requirements such as to perform RHC, a reliable and reproducible 6MWT (eg, use of walking aids such as cane, walker, etc.), or lung function tests.
- Any other criteria as per selexipag Summary of Product Characteristics (SmPC).

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-03-2021
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Uptravi
Generic name:	selexipag
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2020
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	16-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-004887-74-NL
ClinicalTrials.gov	NCT03942211
CCMO	NL69964.056.19

Study results

Date completed:	29-04-2023
Results posted:	16-04-2024

URL result
URL
Type
int
Naam

M2.2 Samenvatting voor de leek
URL

Internal documents
File