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)

Published: 30-06-2020
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Main objective:To assess the effects of selexipag on right ventricular (RV) function in participants with PAH.Secondary objectives:- To further assess the effects of selexipag on RV function using MRI.- To assess the effects of selexipag on disease...

Ethical review	Approved WMO
Status	Completed
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON52455

Source
ToetsingOnline

Brief title
RESTORE

Condition

- Lower respiratory tract disorders (excl obstruction and infection)
- Vascular hypertensive disorders

Synonym
PAH, pulmonary arterial hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Cardiac Magnetic Resonance Imaging (MRI), Pulmonary Arterial Hypertension, RESTORE, Selexipag

Outcome measures

Primary outcome

Change from baseline to Week 26 in RV stroke volume (RVSV) assessed by

pulmonary artery flow magnetic resonance imaging (MRI).

Secondary outcome

Change from baseline to Week 26 assessed by MRI:

• RV end-diastolic volume (RVEDV)

• RV end-systolic volume (RVESV)

• RV ejection fraction (RVEF)

• RV mass

• RV global longitudinal strain (RVGLS)

Change from baseline to Week 26:

• World Health Organization (WHO) Functional Class (FC)

• N-terminal-pro-hormone brain natriuretic peptide (NT-proBNP)

• 6-minute walk distance (6MWD)

• Treatment-emergent adverse events (AEs)

• Serious adverse events (SAEs)

• AEs leading to premature discontinuation of study drug

• AEs of special interest

• Treatment-emergent marked laboratory abnormalities

Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 8 variables:

• Absence of clinical signs of right heart failure

• Absence of symptoms progression

• Absence of syncope

• WHO FC I-II

• 6MWD >440 m

• NT-proBNP <300 ng/L

• Right atrial (RA) area <18 cm2, as determined by echocardiography (Echo)

• Absence of pericardial effusion, as determined by Echo

Change from baseline to Week 26 in number of non-invasive low-risk criteria among the following 3 variables:

• WHO FC I-II

• 6MWD >440 m

• NT-proBNP <300 ng/L

Study description

Background summary

Pulmonary Arterial Hypertension (PAH) is a disease of the small pulmonary arteries that is characterized by vascular proliferation and remodeling. It results in a progressive increase in pulmonary vascular resistance (PVR) and ultimately, right ventricular failure and death. PAH is histologically characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ. The pathogenesis of PAH remains unclear. Advances in understanding the molecular mechanisms involved in this disease suggest that endothelial dysfunction plays a key role. Subjects with PAH have been shown to have a deficiency in PGI2 and PGI2 synthase, which led to the hypothesis that targeting the PGI2 pathway with IP receptor agonists could be beneficial. IV therapy was developed and outcomes for subjects improved. However, due to its short half-life and chemical instability, long-term IV (epoprostenol) therapy requires a permanently implanted central venous catheter and a portable infusion pump, exposing subjects to a series of complications.

Selexipag is the first orally available non-prostanoid IP receptor agonist that has been developed and approved for the treatment of PAH. Selexipag was approved on the basis of long-term clinical efficacy; however, short-term cardiac imaging data on selexipag are lacking.

Study objective

Main objective:
To assess the effects of selexipag on right ventricular (RV) function in participants with PAH.
Secondary objectives:
- To further assess the effects of selexipag on RV function using MRI.
- To assess the effects of selexipag on disease severity and exercise capacity.
- To evaluate the safety and tolerability of selexipag.
- To evaluate the effects of selexipag on risk stratification in PAH.

Study design

This is an open-label, multicenter, single-arm, interventional study to assess the effect of selexipag in adult participants (>=18 to <65 years) with a diagnosis of PAH up to 52 weeks on study intervention.

Intervention

All subjects will be randomized to the study drug Selexipag. Dosing with selexipag will start at 200 µg twice daily (on Day 1, the participant will receive only 1 dose, and at each dose change, the first intake of the new dose should be taken in the evening). The site will call the participant once a week from the end of Week 1 to the end of Week 12 and decide whether to increase the

dose by 200 µg twice daily if possible. Up-titration will be flexible and can be adapted in case of adverse effects that cannot be relieved with symptomatic treatment. In this case, the site may either postpone up-titration by 1 week or down-titrate study drug. The dose reached at end of Week 12 will be considered the participant*s individual maintenance dose (IMD) and will be maintained until EOT (Week 52).

Study burden and risks

Selexipag was previously administered to 1156 adult participants with PAH in randomized, long-term study called GRIPHON. This study was the first study to demonstrate the long-term outcome benefit of selexipag. Selexipag proved to delay disease progression and reduce the risk of hospitalization for PAH.

The short and long-term safety profile of selexipag has been established in PAH patients and is mainly characterized by prostacyclin-associated adverse events (AEs) linked with the mode of action of selexipag (a selective prostacyclin receptor (IP) agonist). AEs typically occur during the initial phase of individualized dose titration, and the susceptibility varies between individuals. Adverse reactions included headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing.

Selexipag has a favorable safety profile with known risks consistent with its mechanism of action. No new observations regarding the safety profile of selexipag have been identified since its approval in the USA on 21 December 2015.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1.Signed informed consent prior to any study-mandated procedure
2.WHO FC II or III. Enrollment will be stratified by WHO FC II or III. Proportion of participants with WHO FC II and WHO FC III are expected to be approximately 40% and 60% respectively.
3.PAH etiology belonging to one of the following groups according to classification:
• Idiopathic PAH
• Heritable PAH
• Drugs or toxins induced
• PAH associated with connective tissue disease
• PAH associated with congenital heart disease, with simple systemic-topulmonary shunt at least 1 year after surgical repair
4.First hemodynamic diagnosis of PAH by right heart catheterization (RHC) within 12 months prior to initiation of selexipag, showing:
• mPAP >=25 mmHg and
• PA wedge pressure (PAWP) or LV end-diastolic pressure <=15 mmHg and
• PVR >5 WU (400 dyn.s.cm-5) and
• RVSV <= 60 mL as shown in RHC (CO/HR)
5. Patients already receiving PAH-specific oral mono or dual therapy (ie, phosphodiesterase type 5 inhibitors (PDE-5i) or soluble guanylate cyclase stimulators (sGCs) and/or ERA) or patients who are not candidates for these therapies. If on oral PAH-specific therapy, treatment has to be stable (ie, no introduction of new therapies or changes in dose) for at least 90 days prior to both ICF signature and Day 1
6.NT-proBNP >=300 ng/L at screening
7.Men or women >=18 years (or the legal age of consent in the jurisdiction in which the study is taking place if greater than 18) and <65 years
8.Women of childbearing potential (Section 10.5) must meet the following criteria:

• Have a negative serum pregnancy test during screening and a negative urine pregnancy test on Day 1, and
• Agree to use reliable methods of contraception from Day 1 to at least 30 days after study intervention discontinuation (Section 10.5), and
• If only using hormonal contraception, have used it for at least 1 month (30 days) before Day 1, and
• Agree to perform monthly pregnancy tests to at least 30 days after study intervention discontinuation
9. 6MWD >=150 m during screening period

Exclusion criteria

1.Prior use of IP-receptor agonist, prostacyclin, or prostacyclin analog. Use of such treatments for vasoreactivity testing is not exclusionary; intermittent use of such treatments for digital ulcers or Raynaud's phenomenon is not exclusionary if stopped >6 months (180 days) prior to Day 1
2.Treatment with strong inhibitors of CYP2C8 (eg, gemfibrozil) within 28 days prior to Day 1
3.Treatment with another investigational drug planned or taken within 12 weeks (84 days) prior to Day 1
4.Cardiopulmonary rehabilitation programs based on exercise between informed consent and expected Week 26 visit date
5.Decompensated cardiac failure requiring hospitalization, emergency room visit or intravenous diuretics in the 6 weeks before informed consent
6.Severe coronary heart disease or unstable angina
7.Cerebrovascular events (eg, transient ischemic attack, stroke) within 3 months prior to Day 1
8.Left atrial volume indexed for body surface area >=43 mL/m2, assessed by Echo or cardiac MRI
9.Myocardial infarction within 6 months prior to Day 1
10.Body mass index >40 kg/m2 or body weight <40 kg
11.Presence of one or more of the following signs of relevant lung disease at any time up to Day 1 - if pulmonary function test results are missing, then exclusion 11 is considered as met • Diffusing capacity of the lung for carbon monoxide <40% of predicted UNLESS computed tomography reveals no or mild interstitial lung disease
• Forced vital capacity <60% of predicted
• Forced expiratory volume in 1 second <60% of predicted
12.Known or suspected pulmonary veno-occlusive disease (PVOD)
13.Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension
14. SBP <90 mmHg at screening or on Day 1
15.Severe renal impairment (estimated creatinine clearance <=30 mL/min/1.73 m2 or serum creatinine >2.5 mg/dL at screening) or ongoing or planned dialysis
16. Known and documented moderate or severe hepatic impairment (with or without

cirrhosis) at screening, defined as Child-Pugh Class C
17.Known or suspected uncontrolled thyroid disease (hypo- or hyperthyroidism)
18.Any hospitalization within 6 weeks prior to informed consent (except elective hospitalizations for surgery or standard monitoring of preexisting conditions that did not worsen)
19.Concomitant life-threatening disease with a life expectancy of less than 12 months
20.Hemoglobin <80 g/L at screening
21.Hypersensitivity to selexipag or any study intervention excipient (mannitol, maize starch, hydroxypropylcellulose, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, carnauba wax, iron oxide red, iron oxide yellow, iron oxide black)
22.Pregnancy, breastfeeding, or intention to become pregnant during the study.
23.Any factor or condition likely to affect compliance with study intervention or visit plan, as judged by the investigator
24.Claustrophobia
25.MRI-incompatible permanent cardiac pacemaker, automatic internal cardioverter
26.Metallic implant (eg, defibrillator, neurostimulator, hearing aid, permanent use of infusion device, dental brace, metal-containing tattoo ink)
27.Severe arrythmia, atrial fibrillation, multiple premature ventricular or atrial contractions, or any other condition that would interfere with proper cardiac gating during MRI

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	04-03-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	30-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
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	EUCTR2019-004783-22-NL
ClinicalTrials.gov	NCT04435782
CCMO	NL74159.056.20

Study results

Date completed:	28-07-2023
Results posted:	19-07-2024

Summary results
Trial ended prematurely

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File