A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH

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The objective of this study is to evaluate the efficacy and safety of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH.

Ethical review	Approved WMO
Status	Completed
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON52318

Source
ToetsingOnline

Brief title
A Phase 3 Study of Sotatercept for the Treatment of PAH

Condition

- Vascular hypertensive disorders

Synonym
Pulmonary Arterial Hypertension; increased blood pressure in arteries in the lungs

Research involving

Human

Sponsors and support

Primary sponsor: Acceleron Pharma Inc.
Source(s) of monetary or material Support: Acceleron

Intervention

Keyword: Phase 3, Pulmonary Arterial Hypertension (PAH), Sotatercept

Outcome measures

Primary outcome

The primary efficacy endpoint is the change in 6MWD at Week 24 versus baseline.

Secondary outcome

Secondary Efficacy Endpoints

Ranked as below:

1. Multicomponent improvement endpoint measured by the proportion of

participants achieving all of the following at Week 24 relative to baseline:

• Improvement in 6MWD (increase >= 30 m)

• Improvement in NT-proBNP (decrease in NT-proBNP >= 30%) or

maintenance/achievement of NT-proBNP level < 300 ng/L

• Improvement in WHO FC or maintenance of WHO FC II

2. Change from baseline in PVR at Week 24

3. Change from baseline in NT-proBNP levels at Week 24

4. Proportion of participants who improve in WHO FC at Week 24 from baseline

5. Time to death or the first occurrence of any of the following clinical

worsening events:

• Worsening-related listing for lung and/or heart transplant

• Need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more

• Need for atrial septostomy

• Hospitalization for worsening of PAH (>= 24 hours)

• Deterioration of PAH defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values:

* Worsened WHO FC

* Decrease in 6MWD by >= 15% confirmed by 2 tests at least 4 hours apart, but no more than 1 week

6. Proportion of participants who maintain or achieve a low risk score at Week 24 versus baseline using the simplified French Risk score calculator

7. Change from baseline in the Physical Impacts domain score of Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) at Week 24

8. Change from baseline in the Cardiopulmonary Symptoms domain score of PAH-SYMPACT® at Week 24

9. Change from baseline in the Cognitive/Emotional Impacts domain score of PAH-SYMPACT® at Week 24

Safety Endpoints:

Safety will be evaluated by collecting the following information:

• Adverse events

• Anti-drug antibodies

• Laboratory assessments (hematology, serum chemistry/FSH, urinalysis)

• Vital signs

• Physical examination

• 12-Lead ECG

Study description

Background summary

Pulmonary Arterial Hypertension is a progressive, fatal disease that causes marked limitations in physical activity and quality of life, even when treated with approved therapies. This Phase 3 study is supported by data from the PULSAR study (Phase 2, NCT03496207), in which participants taking any approved single or combination therapy for PAH were randomized to receive additional sotatercept or placebo for 24 weeks. The PULSAR study demonstrated a statistically significant improvement in its primary endpoint, Pulmonary Vascular Resistance (PVR). Additionally, improvement was observed in 6-Minute Walk Distance (6MWD), NT proBNP, and other endpoints.

Study objective

The objective of this study is to evaluate the efficacy and safety of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) at 24 weeks in adults with PAH.

Study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study.

Intervention

Each study eligible participant will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms for the duration of the DBPC and LTDB Treatment Periods.
• Arm 1: Placebo administered subcutaneously (SC) every 21 days plus background PAH therapy
• Arm 2: Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously (SC) every 21 days plus background PAH therapy

Study burden and risks

This is a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH. Approximately 284 participants will be randomly assigned in a 1:1 ratio to the two study treatment groups sotatercept plus background PAH therapy or Placebo plus background PAH therapy. Patients are asked to undergo the procedures described in schedule of events in the protocol. These procedures include physicial examination, ECG, pulmonary function tests, six minute walk test, ECHO, blood sampling, RHC and questionnaires. Additionally, fertile subjects are asked to use
contraceptives, and female subjects of childbearing potential will have pregnancy tests.
This Phase 3 study is supported by data from the PULSAR study (Phase 2, NCT03496207), in which participants taking any approved single or combination therapy for PAH were randomized to receive additional sotatercept or placebo for 24 weeks. The PULSAR study demonstrated a statistically significant improvement in its primary endpoint, Pulmonary Vascular Resistance (PVR). Additionally, improvement was observed in 6-Minute Walk Distance (6MWD), NT proBNP, and other endpoints.
Treatment with sotatercept in addition to background PAH therapies was well tolerated, with thrombocytopenia and increased hemoglobin levels being the most commonly reported drug-related side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Age >= 18 years
2. Documented diagnostic right heart catheterization (RHC) at any time prior to screening confirming the diagnosis of WHO PAH Group 1 in any of the following subtypes:
• Idiopathic PAH
• Heritable PAH
• Drug/toxin-induced PAH
• PAH associated with CTD
• PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
3. Symptomatic pulmonary hypertension classified as WHO FC II or III
4. Baseline RHC performed during the Screening Period documenting a minimum PVR of >= 5 Wood units (WU) and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of <= 15 mmHg.
5. At stable doses of background PAH therapy and diuretics (i.e., patientspecific dose goal for each therapy already achieved) for at least 90 days prior to screening; for infusion prostacyclins, dose adjustment within 10% of optimal dose is allowed per medical practice.
6. 6MWD >= 150 and <= 500 m repeated twice at screening (measured at least 4 hours apart, but no longer than 1 week), and both values are within 15% of each other (calculated from the highest value)
7. Females of childbearing potential must:
• Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study drug administration; she must agree to ongoing pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug
• If sexually active, have used, and agree to use, highly effective contraception without interruption, for at least 28 days prior to starting the investigational product, during the study (including dose interruptions), and for 16 weeks (112 days) after discontinuation of study treatment
• Refrain from breastfeeding a child or donating blood, eggs, or ovum for the duration of the study and for at least 16 weeks (112 days) after the last dose of study treatment

8. Male participants must:
• Agree to use a condom, defined as a male latex condom or non-latex condom NOT made out of natural (animal) membrane (e.g., polyurethane), during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 16 weeks (112 days) following investigational product discontinuation, even if he has undergone a successful vasectomy
• Refrain from donating blood or sperm for the duration of the study and for 112 days (112 days) after the last dose of study treatment
9. Ability to adhere to study visit schedule and understand and comply with all protocol requirements
10. Ability to understand and provide written informed consent

Exclusion criteria

1. Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH and PAH associated with portal hypertension. Exclusions in PAH Group I should also include schistosomiasis associated PAH and pulmonary veno-occlusive disease
3. Hemoglobin (Hgb) at screening above gender-specific upper limit of normal, per local laboratory test
4. Baseline platelet count < 50,000/mm3 (< 50.0 × 109/L) at screening
5. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mmHg or sitting diastolic blood pressure > 100 mmHg during screening visit after a period of rest
6. Baseline systolic blood pressure < 90 mmHg at screening
7. Pregnant or breastfeeding women
8. Any of the following clinical laboratory values at the screening visit:
• eGFR < 30 mL/min/m2 (as defined by the Modification of Diet in Renal Disease [MDRD] equation)
• Serum alanine aminotransferase, aspartate aminotransferase levels or total bilirubin > 3 × ULN (bilirubin criterion waived if there is a documented history of Gilbert*s syndrome)
9. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 halflives for biologics prior to the date of signed informed consent
10. Prior exposure to sotatercept (ACE-011) or luspatercept (ACE-536) or known allergic reaction to either one
11. History of full pneumonectomy
12. Pulmonary function test (PFT) values of forced vital capacity (FVC) < 60% predicted at the screening visit or within 6 months prior to the screening visit. If PFT is not available, a chest CT scan showing more than mild interstitial lung disease at the screening visit or 1 years prior to it
13. Initiation of an exercise program for cardiopulmonary rehabilitation within

90 days prior to the screening visit or planned initiation during the study (participants who are stable in the maintenance phase of a program and who will continue for the duration of the study are eligible)
14. History of more than mild obstructive sleep apnea that is untreated
15. Known history of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C (with evidence of recent infection and/or active virus replication), defined as mild to severe hepatic impairment (Child-Pugh Class A-C).
16. History of restrictive, constrictive or congestive cardiomyopathy
17. History of atrial septostomy within 180 days prior to the screening visit
18 Electrocardiogram (ECG) with Fridericia's corrected QT interval (QTcF) >500 ms during Screening Period.
19 Personal or family history of long QT syndrome (LQTS) or sudden cardiac death
20Left ventricular ejection fraction (LVEF) < 45% on historical ECHO within 6 months prior to the screening visit
21 Any current or prior history of symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) in the past 6 months prior to the screening visit. Note: Anginal pain can be ignored as an exclusion criterion if coronary angiography shows no obstructions
22 Cerebrovascular accident within 3 months prior to the screening visit
23 Acutely decompensated heart failure within 30 days prior to the screening visit, as per investigator assessment
24 Significant (>= 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease.
25 Received intravenous inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the screening visit.

Study design

Design

Study phase:	3
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):	13-01-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sotatercept (ActRIIA-IgG1Fc)
Generic name:	-

Ethics review

Approved WMO Date:	17-02-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-03-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	07-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2020-004142-11-NL
ClinicalTrials.gov	NCT04576988
CCMO	NL76294.028.21

Study results

Date completed: 24-10-2022

Results posted: 12-10-2023

Actual enrolment: 2

First publication
12-10-2023