A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality

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This study has been transitioned to CTIS with ID 2023-509140-10-00 check the CTIS register for the current data. The objective of this study is to evaluate the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus...

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

Summary

ID

NL-OMON54241

Source
ToetsingOnline

Brief title
Zenith

Condition

- Pulmonary vascular disorders

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

Research involving
Human

Sponsors and support

Primary sponsor: Acceleron Pharma Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA
Source(s) of monetary or material Support: Acceleron

Intervention

Keyword: Phase 3, Pulmonary arterial hypertension, Sotatercept

Outcome measures

Primary outcome

The primary efficacy endpoint is the time to first event of all-cause death,

lung transplantation, or PAH worsening-related hospitalization of >= 24 hours.

All events will be adjudicated by a blinded, independent committee of clinical

experts.

Secondary outcome

The secondary endpoints are ranked as follows:

1. Overall survival

2. Transplant-free survival

3. Proportion of participants who experienced a mortality event at EOS

4. Change from baseline in REVEAL Lite 2.0 risk score at Week 24

5. Proportion of participants achieving a low or intermediate (<= 7) REVEAL Lite

2.0 risk score at Week 24

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

7. Change from baseline in mean pulmonary artery pressure (mPAP) at Week 24

8. Change from baseline in PVR at Week 24

9. Proportion of participants who improve in WHO FC at the end of the DBPC

Treatment Period

10. Change from baseline in 6MWD at Week 24

11. Change from baseline in cardiac output (CO) at Week 24

12. Change from baseline in EuroQoL-5 dimensions scale 5 levels (EQ-5D-5L)

index score at Week 24

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 Phase 2 Study A011-09 (PULSAR; 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, improvements were observed in 6 minute walk distance (6MWD), N terminal prohormone B-type natriuretic peptide (NT proBNP), and other endpoints.

Study objective

This study has been transitioned to CTIS with ID 2023-509140-10-00 check the CTIS register for the current data.

The objective of this study is to evaluate the effects of sotatercept treatment (plus maximum tolerated background PAH therapy) versus placebo (plus maximum tolerated background PAH therapy) on time to first event of all cause death, lung transplantation, or PAH worsening-related hospitalization of >= 24 hours, in participants with WHO FC III or FC IV PAH at high risk of mortality.

Study design

A phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel

group study

Intervention

Each study-eligible participant will be randomized in a 1:1 ratio to one of the 2 treatment arms prior to starting the DBPC Treatment Period.
• 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 SC every 21 days plus background PAH therapy

Study burden and risks

The following side effects of sotatercept are very common (reported in more than 10% of participants in placebo controlled studies for different participant groups):
Headache Increase in red blood cells, hemoglobin, hematocrit (increase numbers of red blood cells in the bloodstream)
Increased blood pressure/hypertension Viral upper respiratory tract infection/ pneumonia (chest infection)
Dizziness Hot flush
Low level of white blood cells Bladder infection
Low level of platelets
(blood cells involved in forming blood clots) Feeling of physical weakness or less strength
Feeling tired Sensation of numbness or tingling of the skin
Muscle spasms Fever
Arm and/or leg injury/pain Vomiting
Back pain Dehydration
Muscular chest pain Nausea
Increase in blood creatinine (worsening of kidney function) Shortness of breath
Low blood pressure Swelling in the legs
Diarrhea Decrease in levels of blood potassium
Telangiectasia (small red, threadlike patterns of blood vessels on the skin)
Nosebleeds

This is not a complete list of all side effects that may occur, as there may be risks or side effects of sotatercept that are unknown or cannot be predicted at this time.

All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

Sotatercept is a protein and therefore the body may make antibodies.

There are also certain risks associated with the use of sotatercept:

During sotatercept research studies, there have been reports of increases in red blood cells, hemoglobin (a molecule in your blood that carries oxygen), and hematocrit (a way to measure amount of red blood cells) as well as increases in blood pressure which might require treatment. An increase in red blood cells may lead to associated events like headache, high blood pressure, blood clotting in your blood vessels, lack of blood flow and oxygen to your brain, damage to organs and eyes, and death. Furthermore, a decrease in white blood cell count and platelet count in cancer studies with sotatercept. These chances might pose a potential risk for infection and bleeding.

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

Eligible participants must meet all of the following inclusion criteria to be

enrolled in the study:
1. Age 18 to 75 years, inclusive
2. Documented diagnostic right heart catheterization 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 PAH classified as WHO FC III or IV
4. REVEAL Lite 2.0 risk score of >= 9
5. Right heart catheterization performed during screening (or within 2 weeks prior to screening, if done at the clinical study site) documenting a minimum PVR of >= 5 Wood units and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of <= 15 mmHg
6. Clinically stable and on stable doses of maximum tolerated (per investigator*s judgment) double or triple background PAH therapies for at least 30 days prior to screening
7. Females of childbearing potential must:
• Have 2 negative urine or serum pregnancy tests as verified by the investigator prior to starting study therapy; must agree to ongoing urine or serum pregnancy testing during the course of the study and until 8 weeks after the last dose of the study drug
• If sexually active with a male partner
- used highly effective contraception without interruption; for at least28 days prior to starting the investigational product AND
- agree to use the same highly effective contraception in combination with a barrier method 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 nonlatex 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 16 weeks (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 PH WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus-associated PAH and PAH associated with portal hypertension
3. Diagnosis of pulmonary veno-occlusive diseases or pulmonary capillary hemangiomatosis or overt signs of capillary and/or venous involvement
4. Hemoglobin at screening above gender-specific upper limit of normal (ULN), per local laboratory test
5. Baseline platelet count < 50,000/mm3 (< 50.0 x 109/L) at screening
6. Baseline systolic blood pressure < 85 mmHg at screening
7. Pregnant or breastfeeding women
8. Serum alanine aminotransferase, aspartate aminotransferase levels or total bilirubin > 3.0 × ULN
9. Currently enrolled in or have completed any other investigational product study within 30 days for small-molecule drugs or within 5 half-lives for biologics prior to the date of signed informed consent
10. Prior exposure to sotatercept or known allergic reaction to sotatercept, its excipients, or luspatercept
11. History of pneumonectomy
12. Untreated more than mild obstructive sleep apnea
13. History of known pericardial constriction
14. History of restrictive or congestive cardiomyopathy
15. Electrocardiogram (ECG) with Fridericia*s corrected QT interval (QTcF) > 500 ms during the Screening Period
16. Personal or family history of long QT syndrome or sudden cardiac death
17. Lening Visitft ventricular ejection fraction < 45% on historical echocardiogram within 1 year prior to the Screening Visit
18. 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
19. Cerebrovascular accident within 3 months prior to the Screening Visit
20. Significant (>= 2+ regurgitation) mitral regurgitation or aortic regurgitation valvular disease
21. Currently on dialysis or anticipated need for dialysis within the next 12 months

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:	Recruiting
Start date (anticipated):	22-08-2022
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-09-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-11-2021
Application type:	First submission
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:	10-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2024
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-06-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2024
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
EU-CTR	CTIS2023-509140-10-00
EudraCT	EUCTR2021-001498-21-NL
ClinicalTrials.gov	NCT04896008
CCMO	NL78790.028.21