A Phase 3, Randomized, Double-blind, Placebo controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients

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The objective of this study is to evaluate the effects of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) on time to clinical worsening (TTCW) in participants who are newly diagnosed with PAH and are...

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

Summary

ID

NL-OMON56236

Source
ToetsingOnline

Brief title
A011-13 Hyperion

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

Intervention

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

Outcome measures

Primary outcome

The primary efficacy endpoint is TTCW, defined as the time from randomization

to the first confirmed morbidity event or death. The events that will comprise

this endpoint include the following:

• All-cause death

• Non-planned PAH-related hospitalization of >= 24 hours in duration

• Atrial septostomy

• Lung transplant

• Deterioration in performance in exercise testing due to PAH, defined as a

decrease in 6MWD from baseline (average of screening) on 2 consecutive tests

(which must be at least 4 hours apart) and at least 1 of the following:

- Worsening of WHO FC from baseline

- Signs/symptoms of increased right heart failure

- Addition of a background PAH therapy or change in the background PAH therapy

delivery route to parenteral

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

experts.

Secondary outcome

The 9 secondary endpoints are ranked as follows:

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 meters [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. Proportion of participants who maintain or achieve a low-risk category of REVEAL Lite 2 risk score at Week 24 versus baseline

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

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

5. Proportion of participants who improve in WHO FC or maintain WHO FC II at 24 weeks from baseline

6. Change from baseline in 6MWD at Week 24

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

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) and the STELLAR study (Phase 3, NCT04576988). In PULSAR, participants taking any approved single or combination therapy for PAH were randomized to receive sotatercept (ACE-011, MK-7962) or placebo for 24 weeks. PULSAR demonstrated a statistically significant improvement in its primary endpoint, pulmonary vascular resistance (PVR). Additionally, improvement was observed in 6-minute walk distance (6MWD), N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, and other endpoints. In STELLAR, participants taking single or combination PAH therapy were randomized to receive sotatercept or placebo for 24 weeks. STELLAR demonstrated a statistically significant and clinically meaningful improvement in its primary endpoint, 6MWD, and achieved statistical significance in 8 of 9 secondary efficacy outcome measures, including improvements in PVR and the World Health Organization (WHO) functional class (FC) [Hoeper, M. M., et al 2023].

Study objective

The objective of this study is to evaluate the effects of sotatercept treatment (plus background PAH therapy) versus placebo (plus background PAH therapy) on time to clinical worsening (TTCW) in participants who are newly diagnosed with PAH and are at intermediate or high risk of disease progression.

Study design

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

Intervention

Each eligible participant will be randomized in a 1:1 ratio to 1 of the following 2 treatment arms during 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, SC every 21 days plus background PAH therapy

Study burden and risks

The study treatment may cause side effects. Side effects can be mild to severe and they can vary from person to person.

Listed below are side effects reported in participants of previous PAH studies :

- Headache
- Diarrhea
- Nosebleeds
- Feeling tired
- Dizziness
- Telangiectasia (small red, threadlike patterns of blood vessels on the skin)
- Increase in red blood cells, hemoglobin, and hematocrit (proportion of red blood cells in the bloodstream)
- Low level of platelets (blood cells involved in forming blood clots)
- Increased blood pressure (hypertension)
- Hot flush
- Rash
- Decrease in levels of blood potassium
- Pain in extremity
- Swelling in the limbs
- Nausea
- Urinary tract infection
- Nasal congestion
- Feeling of physical weakness or less strength
- Sensation of numbness or tingling of the skin
- Muscle spasms
- Back pain
- Fever
- Vomiting
- Dehydration

There are also certain risks associated with the use of sotatercept:
In previous sotatercept studies in patients with PAH, 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.

In previous sotatercept studies in patients with PAH, some participants had a decrease in platelet count. This change may pose a potential risk for bruising and bleeding. You will be tested throughout the study to monitor for platelet counts.

As with any drug, it is possible that participants have allergic reactions.

Sotatercept is a protein and therefore your body may make antibodies to sotatercept.

Right Heart Catheterization
While uncommon, the risks of RHC include air leak in the lungs and perforation of major vessels with possible bleeding or irregular heartbeat. Participants will receive radiation exposure as images are taken of the heart and blood vessels.

Radiation Exposures:

For RHC tests we use X-rays. In this study, participants will receive approximately 7.5 mSv of radiation in total if they require a RHC.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Age >= 18 years
2. Documented diagnostic right heart catheterization (RHC) within 12 months of screening documenting a minimum PVR of >= 4 Wood units and pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of <= 15 mmHg, with 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 II or III
4. Either REVEAL Lite 2 risk score >= 6 or COMPERA 2.0 risk score >= 2 (intermediate-low-risk or above)
5. Diagnosis of PAH within 12 months of screening and on stable doses of a double or triple combination of background PAH therapies and diuretics (if any) for at least 90 days prior to screening. Background PAH therapy and diuretics are further defined in Section 7.2.
6. 6MWD >= 150 m repeated twice at screening at least 4 hours apart, but no longer than 1 week apart, and both values are within 15% of each other (calculated from the highest value)
7. Females of childbearing potential (as defined in Appendix 4) must meet the following criteria:
• Have 2 negative urine or serum pregnancy tests as verified by the investigator during the Screening Period;
• Agree to ongoing pregnancy testing (either urine or serum) 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 least 28 days prior to starting the investigational product AND
- Agreed 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 meet the following criteria:
• 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 documented informed consent

Exclusion criteria

1. Diagnosis of pulmonary hypertension (PH) WHO Groups 2, 3, 4, or 5
2. Diagnosis of the following PAH Group 1 subtypes: human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, pulmonary veno occlusive disease and pulmonary capillary hemangiomatosis
3. Hgb at screening above gender-specific upper limit of normal (ULN), per local laboratory test
4. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 180 mmHg or sitting diastolic BP > 110 mmHg during the Screening Visit after a period of rest
5. Baseline systolic BP < 90 mmHg at screening
6. Pregnant or breastfeeding women
7. Any of the following clinical laboratory values at the Screening Visit:
• Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 (as defined by MDRD equation)
• Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels > 3 × ULN (For United Kingdom [UK], refer to the specific requirement in Appendix 6)
• Platelet count < 50,000/mm3 (< 50.0 × 109/L)
8. Currently enrolled in or have completed any other investigational product study within 30 days for small molecule drugs or within 5 half-lives for investigational biologics prior to the date of documented informed consent
9. Known allergic reaction to sotatercept (ACE-011), its excipients, or luspatercept
10. History of pneumonectomy
11. Pulmonary function test values of forced vital capacity < 60% predicted within 1 year prior to the Screening Visit
12. Stopped receiving any PH chronic general supportive therapy (e.g., diuretics, oxygen, anticoagulants, and digoxin) within 60 days prior to the Screening Visit
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. Untreated more than mild obstructive sleep apnea

15. History of known pericardial constriction
16. History of restrictive cardiomyopathy
17. History of atrial septostomy within 180 days prior to the Screening Visit
18. Electrocardiogram (ECG) with Fridericia*s corrected QT interval > 500 ms during the Screening Period (For UK and South Korea, refer to the specific requirements in Appendix 6).
19. Personal or family history of long QT syndrome or sudden cardiac death
20. Left ventricular ejection fraction < 50% documented by a historical echocardiograph (ECHO) or cardiac magnetic resonance imaging (MRI) within the last 12 months prior to screening (if there is more than 1 assessment of left ventricular ejection fraction (LVEF), the value from the most recent measurement should be used in assessing eligibility)
21. Coronary artery disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months prior to the Screening Visit
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, and vasopressin) within 30 days prior to the Screening Visit
26. Active malignancy with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or prostate cancer that is not currently or expected, during the study, to be treated with radiation therapy, chemotherapy, and/or surgical intervention, or hormonal treatment.

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):	14-09-2022
Enrollment:	14
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Sotatercept (ActRIIA-IgG1Fc)
Generic name:	-

Ethics review

Approved WMO Date:	30-08-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-10-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	21-03-2022
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:	21-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	22-12-2023
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:	06-06-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-07-2024
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
EudraCT	EUCTR2021-000199-12-NL
ClinicalTrials.gov	NCT04811092

Register	ID
CCMO	NL77852.028.21