Phase 2 Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Sotatercept (MK-7962) in Children from 1 to Less Than 18 Years of Age With PAH on Standard of Care

Published: 09-11-2022
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2023-504861-22-00 check the CTIS register for the current data. This study will assess the safety and tolerability of sotatercept in pediatric participants with PAH WHO Group 1 who receive PAH...

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

Summary

ID

NL-OMON53701

Source
ToetsingOnline

Brief title
MK7962-008

Condition

- Vascular hypertensive disorders

Synonym
pulmonary arterial hypertension

Research involving

Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme (MSD)

Intervention

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

Outcome measures

Primary outcome

• To evaluate the safety and tolerability of sotatercept over 24 weeks of

treatment

• To evaluate the PK of sotatercept over 24 weeks of treatment

Secondary outcome

• To evaluate the pharmacodynamics of sotatercept over 24 weeks of treatment

Study description

Background summary

PAH applies to a group of diseases causing a progressive increase in PVR, resulting in RV dysfunction and, ultimately, heart failure as well as premature death.

Study objective

This study has been transitioned to CTIS with ID 2023-504861-22-00 check the CTIS register for the current data.

This study will assess the safety and tolerability of sotatercept in pediatric participants with PAH WHO Group 1 who receive PAH background therapy. In the absence of treatment, the majority of patients succumb to heart failure within a few years of diagnosis. There is currently no pharmacological cure for PAH. Current background PAH therapy involves increasing blood flow through the pulmonary vasculature via pharmacologic manipulation of various pathways to

relieve symptoms and slow clinical worsening of the disease. There is an unmet need for additional PAH therapies because despite available options, the disease continues to progress in most patients. Through a novel mechanism of action, sotatercept targets an imbalance in activin/GDF and BMP pathway signaling, opening a new treatment paradigm for PAH.

Genetic mutations in the BMPR2 are associated with the majority of cases of the familial form of PAH and approximately 25% of IPAH cases. Specifically, impairment of the BMPR2-associated signal pathway appears to lead to uncontrolled proliferation of pulmonary VSMCs, the principal cause of PAH. These data strongly suggest a key role of TGF-β family members in the pathogenesis of PAH. Sotatercept acts to block activin ligands and GDFs, may attenuate BMPs, and improves pulmonary vascular remodeling by restoring balance to Smad signaling. Sotatercept binds to select ligands in the TGF-β superfamily to suppress their signaling and restore balance between the opposing growth promoting activin/GDF and growth-inhibiting BMP pathways.

Study design

This is a Phase 2, interventional, multicenter, open-label, single-group assignment study in participants >=1 to <18 years of age with PAH WHO Group 1 (based on documented, historic diagnostic RHC). PAH WHO Group 1 consists of IPAH, heritable PAH, drug/toxin-induced PAH, PAH associated with CTD, PAH-CHD with shunt closure more than 6 months before the Screening Period, and PAH associated with coincidental shunt. Eligible participants will have PAH classified as WHO FC I or symptomatic PAH classified as WHO FC II to IV.

Four age-defined cohorts will be sequentially enrolled from oldest to youngest, as follows:
• Cohort 1: >=12 to <18 years (N=12)
• Cohort 2: >=6 to <12 years (N=12)
• Cohort 3: >=2 to <6 years (N=12)
• Cohort 4: >=1 to <2 years (N=6)
Each subsequent younger-aged cohort will not begin enrollment until safety and PK data (after 4 dosing visits) have been evaluated for, at a minimum, the first 4 PK-evaluable participants (defined as participants with at least 1 evaluable postbaseline sample) in the immediately preceding, older-aged cohort. The dose of sotatercept for each subsequent younger-aged cohort may be adjusted to achieve similar exposures to those observed in adults based on review of safety data by the eDMC and PK and safety data by the Sponsor*s siDMC.

Intervention

N/A

Study burden and risks

For this study, patients will be exposed to invasive procedures such as blood collection, physical examination, ECG monitoring, study medication administration, parents or guardians will be asked to answer questions about medication and the health status of their child and will be requested to visit the hospital for check-up visits and / or a final telephone contact.

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. However, data from clinical studies in children are limited.

In the PULSAR study, more than 90% of participants received a dual or triple PAH background therapy at baseline, targeting multiple existing therapeutic pathways. Treatment with sotatercept led to hemodynamic and functional improvements in these participants, including those who received maximum PAH therapy with combinations of two/three medications and intravenous prostacyclin. The results of PULSAR showed conclusive, preliminary evidence of the safety and efficacy of sotatercept in adults. Because the underlying pathobiology is similar between adult and pediatric patients with PAH WHO group 1, and because the protein targets bound by sotatercept are identical in all people, the effects of sotatercept in pediatric patients are expected to be similar to those in adults.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

The main inclusion criteria are listed here. For a complete list of inclusion please refer to the research protocol.
1. Male or female participants >=1 to <18 years of age at the time of providing documented informed consent/assent:
• Cohort 1: Age >=12 to <18 years of age
• Cohort 2: Age >=6 to <12 years of age
• Cohort 3: Age >=2 to <6 years of age
• Cohort 4: Age >=1 to <2 years of age
2. Documented, historic diagnostic RHC any time before Screening confirming the diagnosis of PAH WHO Group 1.
3. For the above-mentioned historical RHC, diagnostic criteria will be mean pulmonary artery pressure >=20 mmHg at rest, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure <=15 mmHg, and PVR indexed to body surface area, >= 3.0 WU.m2
4. PAH classified as WHO FC I or symptomatic PAH classified as WHO FC II to IV
5. Participants must be on a stable dose(s) of background PAH therapy
6. Arterial BP at Screening within normal range for the age, gender, and height percentiles
7. Left ventricular ejection fraction >=50% on the ECHO at Screening

Exclusion criteria

The main exclusion criteria are listed here. For a complete list of exclusion please refer to the research protocol.
1. History of left-sided heart disease, including valvular disease (eg, moderate or greater mitral or aortic regurgitation or stenosis), left ventricular outflow tract obstruction, and/or left heart failure (eg, restrictive or dilated cardiomyopathy)

2 Severe (as based on the opinion of the investigator) congenital or developmental abnormalities of the lung, thorax, and/or diaphragm
3. History of Eisenmenger syndrome, Potts shunt, atrial septostomy within 180 days prior to the screening visit, or atrial septostomy with Eisenmenger physiology
4. Unrepaired or residual cardiac shunt with Qp/Qs >1.5
5. Diagnosis of pulmonary veno-occlusive diseases, pulmonary capillary hemangiomatosis, or overt signs of capillary and/or venous involvement
6. PAH associated with portal hypertension
7. Known visceral (lung, liver, or brain) arteriovenous malformation(s)
8. History of full or partial pneumonectomy
9. Untreated more than mild obstructive sleep apnea
10. History of known pericardial constriction
11. Family history of sudden cardiac death or long QT syndrome
12. Any current or prior history of symptomatic coronary disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or cardiac anginal chest pain) within 6 months before Screening
13. Cerebrovascular accident within 3 months before Screening
14. Prior exposure to sotatercept or luspatercept or has had an allergic reaction to any of their excipients
15. Currently enrolled in or has completed a study with any other investigational products (small molecule drugs or biologics) within 30 days or 5 half-lives of that investigational product (whichever is longer) before Screening

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-12-2023
Enrollment:	1

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sotatercept
Generic name:	Sotatercept

Ethics review

Approved WMO Date:	09-11-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-01-2023
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-09-2023
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	CTIS2023-504861-22-00
EudraCT	EUCTR2022-000478-25-NL
ClinicalTrials.gov	NCT05587712
CCMO	NL82408.028.22