An open-label extension study to investigate efficacy, safety and tolerability of LTP001 in participants with pulmonary arterial hypertension

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To assess the long term safety of LTP001 in participants with pulmonary arterial hypertension (PAH).

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

Summary

ID

NL-OMON53913

Source
ToetsingOnline

Brief title
CLTP001A12201E1

Condition

- Pulmonary vascular disorders

Synonym
increases blood pressure in the pulmonary circulation

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter

van dit onderzoek)

Intervention

Keyword: Efficacy, LTP001, Pulmonary arterial hypertension, Safety

Outcome measures

Primary outcome

To assess the long-term safety of LTP001 in participants with pulmonary arterial hypertension (PAH), based on AEs, SAEs, vital signs, ECGs, safety laboratory measurements.

Secondary outcome

- To assess the effect of LTP001 on hemodynamic parameters derived from RHC

- To assess the effect of LTP001 on the 6MWD

- To assess the effect of LTP001 on measurements of right ventricular function

- To assess the impact of LTP001 on Time to Clinical Worsening.

- To assess the impact of LTP001 on patient reported outcomes.

- To assess the impact of LTP001 on the N-terminal fragment of the prohormone B-type natriuretic peptide

Study description

Background summary

PAH is an orphan disease characterized by chronic elevation in pulmonary arterial pressure, which eventually leads to remodeling of the pulmonary vasculature, followed by right-sided heart failure.
LTP001 is a highly selective and potent, orally administered small molecule designed to inhibit the SMAD-specific E3 ubiquitin protein ligase 1 (SMURF1). SMURF1 is upregulated in vascular cells from patients with pulmonary arterial hypertension (PAH). Increased activity of this ligase is expected to result in impaired bone morphogenic protein (BMP) signaling by degradation of mediators

of the pathway activity.
Impaired BMPR2 signaling is suspected to play an important role within the dysregulation of TGF-beta superfamily pathways that is found in the initiation and progression of PAH. It creates an imbalance in TGFβ/BMP signaling favoring TGFβ and may underlie vascular remodeling in PAH patients with and without BMPR2 mutations. A number of therapeutic strategies have been proposed, beyond the aspiration of gene therapy.
SMURF1 is upregulated in vascular cells from patients with PAH. The role of SMURF1 is to target proteins in the BMP pathway for ubiquitination, thereby triggering degradation of the BMP pathway signal, resulting in vascular smooth muscle cell proliferation and remodeling.

Study objective

To assess the long term safety of LTP001 in participants with pulmonary arterial hypertension (PAH).

Study design

This is a non-randomized, open-label extension study over 52 weeks with LTP001 without a control treatment arm. Participants will be presented the opportunity to consider the extension study at the End of Treatment (EOT) visit (Week 25) of the parent study CLTP001A12201. The investigator will assess if the participant will continue by verifying that the participant has completed the parent study as planned. Moreover, at the EOT the investigator will determine the eligibility for the extension study (i.e. that none of the treatment discontinuation criteria were met and that the assessments at the EOT of the parent efficacy study were completed according to the parent protocol). The investigator may request information on the treatment of the parent study if it is medically required to determine if the patient should continue in the extension study. The treatment shall only be disclosed when all EOT data of the parent study have been entered in the eCRF. The patient may directly continue into the extension study.
The safety and efficacy of LTP001 will be checked at the following visits: Weeks 5, 13, 26, 39 and 52, as specified in the Assessment Schedule. Safety and tolerability assessments will take place at each visit. RHC will be performed at week 26, 6MWT and echocardiography will be assessed at Weeks 26 and 52. PAH-SYMPACT and emPHasis-10 will be collected for 7 days intervals with the seventh day of collection occurring within the allotted visit window for all Treatment visits (Weeks 5, 13, 26, 39 and 52). Following the end of treatment period, participants will have one safety follow-up phone call approximately 30 days after the end of treatment visit at Week 52.

Intervention

LTP001 6mg once dayly

Study burden and risks

Minimaal 6 bezoeken en 1 telefonisch contact. Totale studietijd is 53 weken.

Lichamelijk onderzoek: 5 keer
ECG: 5 keer
Rechter hart katheterisatie: 1 keer
Echocardiografie: 2 keer
6 min. loop test: 2 keer
Vragenlijsten: 5 keer
Bloedafnames: 5 keer

Contacts

Public
Novartis

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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

• Written informed consent must be obtained before any assessment is performed.
• Participant is currently completing the Novartis-sponsored study CLTP001A12201 in PAH and completed key efficacy and safety procedures up to the end of treatment of the parent study, without
meeting discontinuation criteria in the parent study.
• Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
• Participant currently has no evidence of treatment failure, as determined by the investigator, following previous treatment.
• In the opinion of the Investigator the participant would benefit from LTP001 treatment.

Exclusion criteria

• History of hypersensitivity to the study treatment.
• Required or planned transplant or heart/lung surgery.
• Acute or chronic impairment (other than dyspnea), which would limit the ability to comply with study requirements, including interference with physical activity or execution of study procedures such as 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, need for
walking aids).
• Permanent discontinuation of Novartis drug in the parent study due to toxicity or disease progression, non-compliance to study procedures, withdrawal of consent or any other reason.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	17-05-2023
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	LTP001
Generic name:	LTP001

Ethics review

Approved WMO Date:	16-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2024
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	EUCTR2022-002007-38-NL
CCMO	NL83165.056.22