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Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CLTP001A12201E1 / NCT05764265

Version Number: v01 (Clean)

Compound: LTP001

Brief Title: Extension study of efficacy and safety of LTP001 in pulmonary arterial hypertension participants

Study Phase: IIa

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): 2022-002007-38

Approval Date: 30-Jan-2023 (content final)

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Amendment 01 (January 2023)

Amendment rationale

The primary purpose of this amendment is to incorporate safety follow-up visits at Weeks 9 and 17 in response to feedback received by Health Authorities.

The protocol appendix and Safety Assessments table was updated with further guidance for renal alert criteria and follow-up guidelines.

Inclusion criterion #4 was removed to avoid the exclusion of subjects who may have progressed on placebo.

This amendment also corrects for administrative inconsistencies and adds further protocol clarifications to ensure data quality.

Changes to the protocol

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

Extension study of efficacy and safety of LTP001 in pulmonary arterial hypertension participants

Purpose:

The purpose of this study is to explore the efficacy and safety of LTP001 in participants with pulmonary arterial hypertension to determine if LTP001 has an adequate clinical profile to warrant further clinical development in this indication.

Study Indication /Medical Condition:

Pulmonary arterial hypertension

Treatment type:

Drug

Study type:

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary	
• To assess the long-term safety of LTP001 in participants with pulmonary arterial hypertension (PAH).	• AEs, SAEs, vital signs, ECGs, safety laboratory measurements
Secondary	
• To assess the effect of LTP001 on the 6MWD	• Change in 6MWD from baseline over time
• To evaluate the effect of LTP001 on hemodynamic parameters derived from RHC including PVR, RA pressures, mean PA pressure, PCWP, CO, SVR.	• Change from baseline over time for each parameter

Objectives	**Endpoints**
• To assess the effect of LTP001 on measurements of right ventricular function (RVF) in participants with PAH	• Change from baseline in tricuspid annular plane systolic excursion (TAPSE) by echocardiography • Change from baseline in tricuspid annular systolic velocity (TASV) by echocardiography • Change from baseline of peak velocity of excursion (RV S') by echocardiography • Change from baseline in fractional area change (FAC) by echocardiography
• To assess the impact of LTP001 on patient reported outcomes (PRO) in participants with PAH.	• Change from baseline in EmPHasis-10 and PAH-SYMPACT
• To assess the impact of LTP001 on Time to Clinical Worsening (TTCW) in participants with PAH.	• Death • Hospital stay (≥ 24 h) due to worsening of PAH. Worsening of PAH is defined by the following right heart failure related signs and symptoms: syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy • Initiation of parenteral prostanoid therapy, chronic oxygen therapy, or any other PAH-specific therapies or need for increase of diuretics for more than 4 weeks due to worsening of PAH • Disease progression (switch in modified New York Heart Association/WHO FC by at least one grade) • Significant drop in 6MWD (15% from baseline or more) due to PAH-worsening
• To assess the impact of LTP001 on the N-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP).	• N-terminal fragment of the prohormone B-type natriuretic peptide
Exploratory	
CCI	

Objectives	Endpoints
CCI	

Trial Design:

Please refer to Section 1.2 Schema for study design figure.

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 of the parent study CLTP001A12201. At the EOT visit of the parent study, 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 study were completed according to the parent protocol). Participants who are eligible and want to participate in the extension study will need sign an informed consent to receive the extension study treatment. As not all assessment results will be available (e.g. lab assessments) at the same visit date, the investigator will re-assess/reconfirm the eligibility as soon as the outstanding results are received. Patients can directly transition into treatment in this extension study without un-blinding the previous treatment in the parent 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 schedule of activities. Safety and tolerability assessments will take place at each visit. 6MWT and echocardiography will be assessed at Weeks 26 and 52. RHC will be assessed at Week 26. PAH-SYMPACT and emPHasis-10 will be collected for 7 day intervals with the seventh day of collection occurring within the allotted visit window for all visits. Participants will have safety follow-up phone calls at Weeks 9 and 17, and may be invited for unscheduled assessments at the site if deemed necessary. Following the end of the treatment period, participants will have one safety follow-up phone call approximately 30 days after the end of treatment visit at Week 56.

The safety and efficacy profile of LTP001 that is observed in this extension study as well as the parent study, CLTP001A12201, will determine continuation of the extension study.

Brief Summary:

The purpose of this study is to measure the long-term safety and efficacy profile of LTP001 in participants with pulmonary arterial hypertension (PAH). The study offers participants who had completed the CLTP001A12201 double-blind parent study in PAH an opportunity to receive LTP001 (whether they were on LTP001 or not). Unblinding of the treatment received in CLTP001A12201 is not planned.

- The study duration will be up to 54 weeks.
- The treatment duration will be up to 52 weeks.

- The visit frequency will include visits at weeks 1, 5, 13, 26, 39, 52, and 56.

Treatment of interest

The treatment of interest is LTP001 [redacted] mg daily on top of allowed standard of care treatment for PAH. The dose of the allowed concomitant medication should remain stable during the trial.

Number of Participants:

The study population is comprised of male and female adults with PAH. A total of approximately 40 participants are planned to complete the parent study CLTP001A12201 and meet the study entry criteria for this open label extension study.

Key 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.
- In the opinion of the Investigator the participant would benefit from LTP001 treatment.

Key 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.

Treatment Groups:

Active treatment: LTP001 administered as [redacted] mg once daily [redacted] ([redacted]). Investigational study treatment dose adjustments and/or interruptions are not permitted.

Data Monitoring/Other Committee:

Yes; the DMC instituted for the parent study will also receive data from this extension study (see Section 10.1.4 Committees Structure).

Key words:

Pulmonary arterial hypertension, pulmonary vascular resistance, 6 minute walk distance, time to clinical worsening, SMURF1 inhibitor, echocardiography, patient reported outcomes

1.2 Schema

Figure 1-1 Study Schema

1.3 Assessment Schedule

The Assessment Schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to complete the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on the CRF.

PRO measures must be completed before any assessments are performed at any given visit.

As per Section 4.5, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits), alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	**Baseline**			**Extension Treatment Up To Month 12**						
Visit Name	**Transition Period**			**Treatment**					**EOT**	**Post Study Safety Contact**
Visit Numbers[1]	**1**[2]	**100**[2]	**110**		**120**		**130**	**140**	**150**	
Days	**-14 to -1**	**1**	**29 ±7**	**57 ±10**	**85 ±10**	**113 ±10**	**176 ±10**	**267 ±10**	**358 ±10**	**Last treatment +30 -0 +7**
Weeks	**-2 to -1**	**1**	**5 ±1**	**9 ±2**	**13 ±2**	**17 ±2**	**26 ±2**	**39 ±2**	**52 ±2**	**57 -0 +1**
Informed consent[3,4]	X									
Inclusion / Exclusion criteria	X									
Physical Examination			S	S[8]	S	S[8]	S	S	S	
Body Weight			X	X[8]	X	X[8]	X	X	X	
Body Temperature			X	X[8]	X	X[8]	X	X	X	
Blood Pressure and Pulse Rate			X	X[8]	X	X[8]	X	X	X	
Electrocardiogram (ECG)			X	X[8]	X	X[8]	X	X	X	
Dose administration[5]		X	X	X[8]	X	X[8]	X	X	X	
Drug dispensation		X	X		X		X	X		
Collect study medication/ perform drug accountability[5]			X	X[8]	X	X[8]	X	X	X	
Urinalysis			X	X[8]	X	X[8]	X	X	X	
Pregnancy and assessments of fertility			S	S[8]	S	S[8]	S	S	S	
Hematology			X	X[8]	X	X[8]	X	X	X	
Clinical Chemistry			X	X[8]	X	X[8]	X	X	X	

Period	**Baseline**			**Extension Treatment Up To Month 12**						
Visit Name	**Transition Period**			**Treatment**					**EOT**	**Post Study Safety Contact**
Visit Numbers[1]	**1**[2]	**100**[2]	**110**		**120**		**130**	**140**	**150**	
Days	**-14 to -1**	**1**	**29 ±7**	**57 ±10**	**85 ±10**	**113 ±10**	**176 ±10**	**267 ±10**	**358 ±10**	**Last treatment +30 -0 +7**
Weeks	**-2 to -1**	**1**	**5 ±1**	**9 ±2**	**13 ±2**	**17 ±2**	**26 ±2**	**39 ±2**	**52 ±2**	**57 -0 +1**
Coagulation Panel			X	X[8]	X	X[8]	X	X	X	
CCI										
NT-proBNP			X		X		X	X	X	
CCI										
emPHasis-10 and PAH-SYMPACT[6]			X[7]		X[7]		X[7]	X[7]	X[7]	
Right Heart Catheterization[4]							X			
6-Minute Walk Test[4]							X		X	
Echocardiogram[4]							X		X	
Concomitant Medications/ Adverse Events		X						X		
Study completion information									X	

Period	**Baseline**			**Extension Treatment Up To Month 12**						
Visit Name	**Transition Period**			**Treatment**					**EOT**	**Post Study Safety Contact**
Visit Numbers[1]	**1**[2]	**100**[2]	**110**		**120**		**130**	**140**	**150**	
Days	**-14 to -1**	**1**	**29 ±7**	**57 ±10**	**85 ±10**	**113 ±10**	**176 ±10**	**267 ±10**	**358 ±10**	**Last treatment +30 -0 +7**
Weeks	**-2 to -1**	**1**	**5 ±1**	**9 ±2**	**13 ±2**	**17 ±2**	**26 ±2**	**39 ±2**	**52 ±2**	**57 -0 +1**
Safety Follow up Call				S		S				S

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Baseline and Day 1 can be on the same day or within a 14-day transition period
[3] CCI [redacted]
[4] Assessment must be performed onsite. All other assessments may be performed at an off-site location.
[5] Collect unused study medication, perform drug accountability (pill count) and document compliance with protocol instructions.
[6] PROs to be completed by participants for 7 consecutive day intervals around each visit from Weeks 5 to 52. The 7th day of collection for each visit should occur during the Visit Window for Weeks 5 to Week 52.
[7] On clinic visit days, PROs are to be the first assessments performed.
[8] Safety follow-up phone call at Weeks 9 and 17 may require unplanned safety assessment, if deemed necessary by the PI. PI may omit safety assessments per their discretion (optional).

2 Introduction

2.1 Study rationale

The purpose of this study is to study the long term safety and efficacy profile of LTP001 in participants with PAH. The study offers participants who had completed the CLTP001A12201 double-blind parent study in PAH an opportunity to stay on or start receiving treatment with LTP001.

2.2 Background

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) (Rothman et al 2016). 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 (Hemnes and Humbert 2017). 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 (Wilkins et al 2018).

SMURF1 is upregulated in vascular cells from patients with PAH (Rothman et al 2016). 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 (Murakami et al 2010 and Zhu et al 1999).

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.

The classes of therapy on the market for PAH (phosphodiesterase type 5 inhibitors (PDE5i), endothelin receptor antagonists (ERAs), soluble guanylate cyclase (sGC) stimulators and prostacyclin analogues and receptor agonists) leave a substantial unmet medical need. Despite significant advances in the understanding of the underlying mechanisms and development of a number of targeted therapies, PAH remains a challenging condition with high morbidity and mortality (Beshay et al 2020).

Therapies that specifically target remodeling of the pulmonary vasculature would be expected to provide significant benefit as add-on to the available standard of care.

In the First in Human (FIH) study of LTP001, healthy participants completed dosing with single doses of LTP001 CCI .CCI

[redacted]

CCI [redacted]

Overall, all doses were well tolerated. For further details, refer to Section 2.3 and the Investigator's Brochure.

CCI [redacted]

[redacted]

2.3 Benefit/Risk assessment

Potential risks are based on the mechanism of action, the nonclinical toxicology data, and the safety data from the FIH study.

LTP001 is the first SMURF1 inhibitor to be developed. Based on current understanding of SMURF1 biology, there are no concerns directly related to this mechanism of action; and, because LTP001 is first-in-class, there are no previously identified clinical safety risks (i.e., no known class effects).

Preclinical data

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

Clinical data

Single doses of LTP001 CCI mg, CCI mg, CCI mg, CCI mg, CCI mg, CCI mg and CCI mg were well tolerated and did not show safety signals for LTP001 in the first in human study.

Multiple doses of LTP001 CCI mg, CCI mg, CCI mg, CCI mg and CCI mg once daily and CCI mg bid were well tolerated. CCI [redacted]

CCI [redacted], clinical laboratory assessments, ECGs, and vital signs did not show significant abnormalities. CCI [redacted]

The risk to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, regular safety data reviews, and pre-specified rules for automatically stopping the study should unanticipated safety issues suddenly arise.

No reproductive toxicology studies have been performed for LTP001. Women of child-bearing potential will be only enrolled if they use highly effective contraception methods.

Additional details about potential risks of LTP001 can be found in the Investigator's Brochure.

Procedural risks

Cardiac catheterization is a safe procedure when performed by an experienced medical team. However, there may be some possible risks such as bleeding, infection, and blood clots. A heart attack or a stroke can happen in very rare situations. Right heart catheterization (RHC) is regularly employed to monitor the course of PAH. RHC may be performed without radiation but for optimal placement of the catheter, the investigator can employ x-ray to double-check the positioning of the catheter when measurements are made. RHC does not employ contrast media. RHC is required to calculate PVR. PVR was the primary efficacy assessment of the

parent study, CLTP001A12201, and is performed at Week 26 in the current study, which allows the assessment of the 1-year effect of LTP001 of those participants who received LTP001 already in the parent study, and the 6-month effect on PVR of those who received placebo in the parent study. This data is considered very important to assess the long-term effect of LTP001 on PVR in patients with PAH.

Other procedures in the study are non-invasive:

Echocardiography or ultrasound imaging of the heart uses high-frequency sound waves to view soft tissues and does not involve ionizing radiation. Ultrasound imaging has been in widespread clinical use globally for over 20 years with an excellent safety record. There are no known adverse safety risks, but ultrasound use does produce slight bioeffects on the body as the tissue heats slightly when the acoustic waves enter the body and can also produce small pockets of gas in tissue. A hand-held transducer is placed on the skin to produce the image and its application will be limited to the region of interest (chest to perform cardiac exam) to minimize any discomfort and risk of cavitation.

Participants are under observation when they perform the 6MWT.

Participants will maintain standard of care treatment for PAH. Should they require a change of PAH directed therapy due to progression of their PAH related symptoms, they will be discontinued from the study unless the investigator judges that the patient benefits from LTP001 treatment despite the need for added PAH therapy and discusses the situation with the Novartis medical lead for the study (Section 6.8.1.1).

LTP001 is, based on its mechanism of action, not likely to interfere with immune-defense and should not impair the response to vaccines. If participants require vaccinations, e. g. against COVID-19, those can be administered according to the applicable vaccination recommendations. Also, treatment with LTP001 is unlikely to increase the risk of being infected with SARS-CoV-2, the virus causing COVID-19.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment or some of the procedures, such as cardiac catheterization, may involve unknown or known risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Potential benefits

PAH is a progressive disease ultimately leading to cardiac failure and death if untreated. Preclinical data suggest that LTP001 may reduce pulmonary artery pressure and thus may control or reverse disease progression. However, the clinical data with LTP001 is still limited. It has been used in a Phase I study in healthy participants. It is used in the parent study, CLTP001A12201, for this extension study as well as in clinical investigations in other indications, such as lung fibrosis. Thus, when this extension study starts, whilst there will be a safety record in healthy and PAH participants, efficacy may not yet be proven in PAH participants.

2.3.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 52 weeks from each participant as part of the study.

The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedule (Table 1-1).

A summary blood log is provided in the central laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the long term safety of LTP001 in participants with pulmonary arterial hypertension (PAH).	• AEs, SAEs, vital signs, ECGs, safety laboratory measurements
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of LTP001 on hemodynamic parameters derived from RHC including PVR, RA pressures, mean PA pressure, PCWP, CO, SVR.	• Change from baseline at week 26 for each parameter
• To assess the effect of LTP001 on the 6MWD	• Change in 6MWD from baseline over time
• To assess the effect of LTP001 on measurements of right ventricular function (RVF) in participants with PAH	• Change from baseline in tricuspid annular plane systolic excursion (TAPSE) by echocardiography Change from baseline in tricuspid annular systolic velocity (TASV) by echocardiography Change from baseline of peak velocity of excursion (RV S') by echocardiography Change from baseline in fractional area change (FAC) by echocardiography
• To assess the impact of LTP001 on patient reported outcomes (PRO) in participants with PAH.	• Change from baseline in EmPHasis-10 and PAH-SYMPACT

Objective(s)	Endpoint(s)
• To assess the impact of LTP001 on Time to Clinical Worsening (TTCW) in participants with PAH.	• Death • Hospital stay (≥ 24 h) due to worsening of PAH. Worsening of PAH is defined by the following right heart failure related signs and symptoms: syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy • Initiation of parenteral prostanoid therapy, chronic oxygen therapy, or any other PAH-specific therapies or need for increase of diuretics for more than 4 weeks due to worsening of PAH • Disease progression (switch in modified New York Heart Association/WHO FC by at least one grade) • Significant drop in 6MWD (15% from baseline or more) due to PAH-worsening
• To assess the impact of LTP001 on the N-terminal fragment of the prohormone B-type natriuetic peptide (NT-proBNP).	• N-terminal fragment of the prohormone B-type natriuetic peptide
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

3.1 Primary estimands

Not applicable

3.2 Secondary estimands

Not applicable

4 Study design

4.1 Overall design

Please refer to Section 1.2 Schema for study design figure.

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 patient may directly continue into the extension study. If the patient does not directly continue in the extension study, the time between the end of treatment assessments in the parent study and the enrollment in the extension study i.e. during the transition period should be kept to a minimum (it should not exceed 14 days).

Participants who are eligible and want to participate in the extension study will need to have signed an informed consent in order to receive the extension study treatment. In case of a direct transition into the extension study after the end of treatment visit in the parent study, as not all assessment results will be available (e.g. the central lab assessments) at the same day the investigator will re-assess/reconfirm the eligibility as soon as outstanding results are received.

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). Participants will have safety follow-up phone calls at Weeks 9 and 17, and may be invited for safety assessment at site if deemed necessary. The PI may exercise their discretion in which safety assessments are required at these optional safety follow-up visits. 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. The duration of the extension study is currently restricted to 52 weeks, but the study may be prolonged (via an amendment to the protocol) if the LTP001 development program in PAH continues and the benefit/risk assessment remains favorable for the patient population studied. The safety and efficacy profile of LTP001 that is observed in this extension study as well as the parent study, CLTP001A12201, will determine continuation of the extension study.

4.1.1 Off-site procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed, not mandated to be performed onsite, at an off-site location, as defined in Table 1-1. A hybrid model is planned for this study incorporating both onsite and off-site visits. The off-site procedures will be utilized in certain countries and sites as determined by protocol needs and based on national and local/site regulations. Participants have the option of

participating in one or more off-site visits, based on their preference and the investigator's discretion.

One or more of the following elements may be implemented to support off-site visits where allowed by national and local regulations:

- Telemedicine
- Off-site Healthcare Professionals (OHP)
- Direct-to-participant shipment of study supplies
- Direct-to-participant shipment of study treatment (refer to Section 6)
- Electronic Source (eSource) Direct Data Capture (DDC)

4.1.1.1 Responsibility of Investigators

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety and wellbeing of participants. This includes the following, but is not limited to:

- the identification, management and reporting of AEs and SAEs are performed in accordance with the protocol and applicable regulations including the review of PROs to identify any unreported AEs or SAEs.
- OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit
- where relevant, the investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination

4.1.1.2 Responsibility of Off-site Healthcare Professionals

OHPs must have the required qualifications, training, and experience to conduct off-site assessments. OHPs are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Conference for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

During an off-site visit, the OHP will conduct drug accountability and send IMP back to the investigational site for review by the field monitor.

The OHPs will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHPs that are not provided by Novartis this must be agreed with Novartis before use.

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

4.1.1.3 Telemedicine

The sponsor has qualified and contracted a third-party vendor to provide a telemedicine platform technology for this study. The selected platform is a validated system complying with relevant ICH E6 GCP guidelines. Trial participants can interact with site personnel using online communication tools built into the platform, enabling the following capabilities:

- Secure videoconferencing which allows the participant, OHP and site personnel to be connected
- Reminders to be automatically sent to participants (e.g. visit or dosing reminders)
- eSource Direct Data Capture (DDC) (see Section 10.1.5.1)

4.2 Scientific rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Open-label	Design is to assess safety, and all participants will receive active treatment
Eligibility	All participants who completed CLTP001A12201 treatment period and have not met study treatment discontinuation criteria are eligible to enroll. At the time of enrollment, efficacy of LTP001 is unknown, therefore all participants who may benefit can enroll in this extension protocol.
Planned off-site procedures	Off-site procedures are planned in this study to minimize burden on participants, and offer them increased flexibility to participate in the study from an off-site location. This has the potential to broaden access to clinical trials for both participants and investigators. The hybrid approach will allow participants to maintain contact with investigator, both in-person during clinic visits and through the telemedicine platform during off-site participation.

4.3 Justification for dose

LTP001 will be administered once daily[redacted] at a dose level of [redacted] mg. This is the same posology as used in the parent study, CLTP001A12201.

In healthy participants, this dose has been shown to be well tolerated at single and multiple dose administrations. [redacted] this dose level should be adequate and provide full efficacy. Further details are provided in the Investigator's Brochure.

4.3.1 Rationale for choice of background therapy

Participants will remain on the same background therapy as in the parent study, CLTP001A12201, (for details please refer to Section 6) and should not be changed during the extension study. Typically, if there is a deterioration of the participant's PAH condition requiring an escalation of concomitant PAH-specific treatment, the participant should be discontinued from the study treatment (for detailed study discontinuation criteria see Section 7.2) and subsequently return for the EOT assessments. However, if the investigator thinks that the participant should remain on study drug the Novartis medical monitor should be contacted to discuss the change of concomitant PAH medication and the reasons why it is thought to be beneficial for the participant to stay on study drug.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

This is an open label extension study, where all participants are planned to receive active treatment with LTP001. No control treatment is planned during this study. This allows all participants to potentially benefit from treatment, if LTP001 yields clinical benefit in PAH.

4.5 Rationale for public health emergency mitigation procedures

In addition to the planned off-site procedures, in the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity may be implemented.

If allowable by a local health authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or additional visits by OHPs to the participant´s home can replace on-site study visits (in addition to the already planned off-site visits), for the duration of the disruption until it is safe for the participant to visit the site again.

Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

There are no prospectively planned interim analyses. Interim analyses may be conducted to support decision-making concerning the current clinical study, the sponsor’s clinical development projects in general, to provide regular safety updates or in case of any safety concerns.

4.7 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

5 Study population

The study population will be comprised of male and female participants with pulmonary arterial hypertension.

Approximately 40 participants are expected to complete parent study CLTP001A12201 and meet the study entry criteria for this open label extension study.

The investigator must ensure that all participants being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator in order that the study population will be representative of all eligible participants.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. 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 core study, without meeting discontinuation criteria in the core study.
3. Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
5. In the opinion of the Investigator would benefit from LTP001 treatment.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. History of hypersensitivity to the study treatment.
2. Sexually active males not committing to condom use precautions: sexually active males must use a condom during intercourse while taking drug and for 24 hours after stopping study medication and should not father a child in this period nor donate sperm. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
3. Required or planned transplant or heart/lung surgery.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and until EOT visit (2 weeks post-last treatment). Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Use of oral, estrogen and progesterone, injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy) or total hysterectomy at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. 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).
7. Permanent discontinuation of Novartis drug in the core efficacy study due to toxicity or disease progression despite active treatment, non-compliance to study procedures, withdrawal of consent or any other reason.

5.3 Lifestyle considerations

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

5.3.1 Meals and dietary restrictions

CCI [redacted]

5.3.1.1 Dietary restrictions and smoking

Participants should be encouraged to maintain a healthy diet and abstain from the use of alcohol or recreational drugs. Change in smoking status from parent study (CLTP001A12201) will be collected as part of the CRF.

5.3.2 Activity

No significant change in physical exercise program from the beginning of the study until after Study Completion evaluation.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Information includes the screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

Table 6-1 Investigational drugs

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (Global or Local)
LTP001 CCI mg	CCI	Oral Use	Open-label, participant-specific kits	Global
LTP001 CCI mg		Oral Use	Open-label, participant-specific kits	Global

6.1.1 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study drug in packaging as described under Study treatment(s) Table 6-1.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Where delivery of IMP directly to a participant's secure off-site location (e.g. home) is permitted by national and local governing regulations then dispatch of IMP from the site to the participant will be performed under the accountability of the Investigator. The provisioning of supply will be for a maximum of a three-month supply. In this case, regular contacts (every 12 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant's health status until the participant's next visit to the study site.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

Since study treatment is administered at home and when at the clinical site, participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

It should be checked at each visit if other concomitant PAH specific therapy has been kept stable as specified in Section 6.8.1.

6.2.3 Instruction for prescribing and taking study treatment

LTP001 should be taken daily at approximately the same time each day CCI . On clinic visit days, the participant should take LTP001 during the clinic visit when instructed by the study staff. 6MWT and RHC assessment should be executed at approximately the same time after drug administration each time (tolerance window +/- 1 hour).

CCI

If vomiting occurs during the course of treatment, participants should not take the study treatment LTP001 again before the next scheduled dose.

Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 12 hours after the approximate time of the usual daily dosing. That day's dose should be omitted and the participant should continue treatment with the next scheduled dose.

The first day the participant is seen by an off-site health professional during the visit window, or the first day of a visit to the clinical site should be the dose recorded in the Dosage Form eCRF.

Novartis will provide the site with a participant study card to hand over to all study participants, which will state that the participant is participating in a clinical study and is receiving an investigational product. This participant study card will also include the contact information of the Study Doctor/Investigative Site. Designated study stuff will instruct study participants to present this card to a medical care provider if they have any medical issues during the course of the study.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

Not applicable

6.3.2 Treatment blinding

Not applicable

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks are not applicable, as the study medication is open-label.

6.4 Study treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Remote treatment administration compliance will be assessed by the off-site healthcare professional and information provided to the Investigator and/or study personnel.

6.4.1 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs). If participants experience a deterioration of their PAH condition, investigators should determine if they need to be treated with additional PAH directed therapy. Study treatment discontinuation criteria as defined in Section 7.1 should be observed.

Medication used to treat AEs must be recorded on the appropriate CRF.

6.5 Dose modification

Investigational study treatment dose adjustments and/or interruptions are not permitted.

6.6 Continued access to study treatment after the end of the study

Not applicable.

6.7 Treatment of overdose

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or continued as per protocol. The participant should be checked for any adverse events and implementation of safety measures (e.g. additional visit for safety assessments/ additional assessments for safety) should be considered. The Novartis medical team, including the medical monitor, should be informed of any overdosing event.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled into the study must be recorded on the appropriate electronic Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

COVID-19 vaccinations and any other vaccinations with registered vaccines are allowed as recommended for the participant population by the applicable regulations and guidelines.

LTP001 is not expected to be an inhibitor of cytochrome P450 enzymes at the exposures following a [redacted] mg dose. CCI [redacted] See Section 6.8.2 for examples of CCI [redacted] which are prohibited for use throughout the study duration. LTP001 is not expected to be an inhibitor of transporters tested to date. LTP001 is not expected to be a victim of transporter inhibition.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

PAH-directed concomitant medication

ERAs, prostacyclin analogues and receptor agonists, sGC stimulators and/or PDE5i for PAH treatment are allowed. The dose(s) should remain unchanged during the study. In case the investigator reduces or increases the dose of a concomitant PAH directed therapy, or stops or starts a concomitant PAH directed therapy, please contact the Novartis medical monitor.

Single administration of medication for diagnostic purposes (such as use for acute vasodilator testing during the RHC procedure) is allowed.

IV prostacyclin analogues: If daily dose is increased by more than 20% change from initial study dose level please inform Novartis medical monitor.

Overall, if an escalation of PAH directed therapy is required consider if this might be related to ineffective study drug treatment (Section 7.1).

Treatment with diuretics is allowed and may be adjusted during the study with the following precautions:

- Need for another diuretic to be added
- A parenteral diuretic is added
- The oral diuretic dose is more than doubled
- Please inform the Novartis medical monitor and consider if the need for such treatment may point to ineffective study drug treatment

Please do not change diuretic treatment within 7 days prior to a RHC assessment unless required for the safety of the participant.

Other medications

COVID-19 vaccinations and any other vaccinations with registered vaccines are allowed as recommended for the participant population by the applicable regulations and guidelines.

LTP001 is not expected to be an inhibitor of cytochrome P450 enzymes at the exposures following a [redacted]mg dose. [redacted].

LTP001 is not expected to be an inhibitor of transporters tested to date. LTP001 is not expected to be a victim of transporter inhibition.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

6.8.2 Prohibited medication

Participants should remain stable on their PAH-specific background therapy during the study. Unless there is intolerance to background therapy (PDE5i, prostacyclin analogues and receptor agonists, ERAs, and sGC stimulators, refer to Section 6.8.1), doses should be kept stable during the study. Note that a required change in PAH-directed therapy due to clinical worsening of PAH might point to lack of efficacy of LTP001 in the patient. Treatment discontinuation should be considered, and appropriate management of the participant with the PAH directed therapy as per the investigator's discretion and the participant's need instituted.

In terms of treatments required for other conditions or adverse events, there are no known drug interaction signals with LTP001 potentially impacting the PK of other drugs at the dose level under investigation and participants should be treated as per the discretion of the investigator. Also there are no known pharmacodynamic adverse interactions with other treatments identified as yet.

CCI

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CCI

Drugs which are known to prolong the QT interval are prohibited for use throughout the study duration.

6.8.3 Rescue medicine

Rescue medication is defined as an additional medication or change in the dose of an existing medication.

A clinical worsening of PAH requiring a change in dose of an existing PAH-specific medication, or the addition of a new PAH-specific medication, may fulfill criteria for discontinuation for study treatment. PAH-specific medications include: all ERAs, PDE5i, sGC stimulators and oral, intravenous or subcutaneous prostacyclin analogues and receptors agonists. For allowed modifications of PAH directed therapies and adjustments of diuretic therapy please refer to Section 6.8.1.

Use of rescue medications must be recorded on the Concomitant medications/Significant non-drug therapies CRF after signing the informed consent.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant decision
- Pregnancy (if the participant decided to terminate the pregnancy, treatment with LTP001 may be resumed after the abortion procedure if desired by the participant and agreed by the investigator and the Novartis medical monitor).
- Any situation in which continued study participation might result in a safety risk to the participant
- Development of heart failure symptoms consistent with pulmonary hypertension WHO Functional Class IV (symptoms at rest; severe symptoms at exercise)
- If organ transplantation becomes necessary during the study treatment
- Atrial septostomy required due to deterioration of PAH
- Deterioration of PAH suggesting ineffectiveness of LTP001 as per the judgement of the investigator
- Adverse event that is graded severe or serious by the investigator and considered study drug related. If the investigator believes it is beneficial for the participant to stay on study drug (e. g. signs of PAH-improvement and adverse event appears well manageable) and the participant wishes to stay on study drug the investigator shall contact the Novartis medical monitor for further discussion.
- If a liver or renal event occurs, follow guidelines outlined in Section 10.5 *(*Appendix 5) and Section 10.6 (Appendix 6) regarding discontinuation of study treatment.

If discontinuation from study treatment occurs due to participant's decision, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information. In those instances where study drug discontinuation criteria were waived as per the exceptions defined above the decision made as well as the rationale for it needs to be documented in writing in the Trial Master File.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Table 1-1).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

7.5 Study stopping rules

Overall study stopping rules

The study will be put on hold if the Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify it.

In these cases, ad hoc internal experts in collaboration with the DMC (and investigators if felt needed) will recommend whether the study can be continued, should be terminated or if other safety measures need to be taken. The ultimate responsibility on the decision to terminate the study is with the sponsor.

The findings and recommendations of the internal experts and DMC (and investigators if felt needed) will be documented and will be made available to all investigators, their respective Institutional Review Board/Independent Ethics Committee (IRB/IEC), as appropriate.

Any participants currently being dosed will be allowed to continue dosing during the safety review unless otherwise advised by the sponsor, as long as they have not met an individual discontinuation rule or have an ongoing severe or serious adverse event of the same type.

The study may continue following the safety review, if the investigators and Sponsor agree it is safe to proceed. Any restart of the study following a full safety review will be notified to the health authorities or submitted as a substantial amendment, depending on the region and applicable local requirements.

7.6 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision after review of recommendations from applicable board(s) (e. g. DMC)
- Discontinuation of LTP001 development in PAH

- LTP001 fails to show adequate efficacy and safety profile in the ongoing PAH studies in the population studied

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3 Assessment Schedule. Protocol waivers or exemptions are not allowed.
  - Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
  - Adherence to the study design requirements, including those specified in Section 1.3 Assessment Schedule, is essential and required for study conduct.
  - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

Participants are only allowed to join this trial if they have successfully completed the treatment phase of CLTP001A12201, meet all of the inclusion/exclusion criteria, and have signed the informed consent for this trial.

8.2 Participant demographics/other baseline characteristics

The demographic information from the subset of patients that enter the extension study from the parent study CLTP001A12201 will be used for demographics and baseline characteristics. When applicable (i.e., following a significant enrollment delay from the parentstudy end of treatment visit to the first visit of the extension study), study participants will be asked for any changes of their medical conditions, concomitant medication from the last visit of the parent study.

8.3 Efficacy assessments

Pharmacodynamic samples will be collected at the time-points defined in the Assessment Schedule (Table 1-1). Pharmacodynamic samples includes the following assessments:

NT-proBNP

CCI [redacted]

CCI

Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing, and shipment. Pharmacodynamic (PD) samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

8.3.1 Echocardiography

For the assessment of the impact of LTP001 on right heart structure and function, echocardiography will be performed at the time specified in the Assessment Schedule (Table 1-1).

The following parameters will be assessed:

- Tricuspid annular plane systolic excursion (TAPSE)
- Tricuspid annular systolic velocity (TASV)
- Peak velocity of excursion (RV S')
- Fractional area change (FAC)
- CCI

In all participants, the baseline and follow-up imaging will be performed where possible using the same ultrasound scanner and technologist.

The methods for assessment and recording are specified in the imaging charter and imaging manual, also known as the subject scanning guide. All echocardiography images will be centrally read by an imaging vendor.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers. Incidental findings are beyond the scope of central imaging vendor. If an investigator/radiologist recognizes any incidental finding in the images during the course of conducting the clinical trial, the investigator should follow up as part of his/her duty of care to ensure the safety and well-being of the participant.

8.3.2 Right heart catheterization

The RHC assessment is performed to assess several hemodynamic variables in pulmonary hypertension, including mPAP, PCWP, CO, PVR, and systemic vascular resistance (SVR). The RHC Assessments Recommendation Manual provides further instruction on performing the RHC.

- RHC will be performed according to the local hospital procedures. Concomitant PAH medications that could affect hemodynamic measurements need to be taken on a standard schedule relative to the timing of the RHC. When possible, these medications should be taken at least 60 minutes prior to the start of the procedure. Exact timing of dosing of study drug should be recorded in the source document for catheterization. The timing of a participant's concomitant medication and study treatment relative to catheterization should be the same for the subsequent catheterization (tolerance window +/- 1 hour).

- The following hemodynamic parameters will be assessed when the participant is in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the participant is breathing ambient air or oxygen:
  - RA, mPAP, PCWP, systolic and diastolic blood pressure, HR
  - CO (measured in triplicate preferably by the thermodilution technique)
  - Mixed venous blood gas measurement

In all cases, the same technique must be used as was used in the parent study, CLTP001A12201.

- The following parameters will be derived from the CO measurement:
  - SVR in dyn·s/cm^{-5}
  - PVR in dyn·s/cm^{-5}

8.3.3 6-Minute Walk Test

A standardized 6MWT will be performed considering the guidance for the test procedures described by ERS and ATS guidelines (Section 11). The 6MWT measures how many meters a person can walk in 6 minutes. Refer to 6MWT Instructions Manual for further details.

For the Borg score component, the participant will answer questions on a scale of one to ten in order to determine the participant's shortness of breath before the 6MWT. As soon as the test is complete, the participant will be asked to sit down and the SaO2, HR and Borg score values will be recorded.

Resting values of oxygen saturation (%), heart rate (b/min), blood pressure and Borg score will be recorded in the eCRF before the test, at the end of the test and two minutes after the end of the test. Total distance walked (meters), the number and duration of any stops, and whether the participant completed the test will also be recorded in the eCRF.

Requirement of rescue medication including oxygen therapy and any adverse events occurring during the 6MWT will be recorded. If the participant is on chronic oxygen therapy, oxygen should be given at the standard rate (and at the same rate during each 6MWT procedure) or as directed by the investigator.

Single 6MWTs will be performed according the Assessment Schedule (Table 1-1). Every attempt should be made to conduct the 6MWT at about the same time of day.

8.3.4 Appropriateness of efficacy assessments

- The right heart catheterization allows an estimation of the progression of PAH by measuring the right heart and pulmonary arterial pressures as well as cardiac function. RHC is commonly employed in studies with PAH as a sensitive functional assessment to assess disease progression. In the scope of the current study it allows the detection of improvement within a small study population.
- Echocardiography is a commonly used technique to measure cardiac structure and functional parameters, is non-invasive and such allows more frequent monitoring without procedural risks.
- The 6MWT is a well standardized and simple test to assess physical performance.

8.4 Safety assessments

Safety assessments are specified below with the Assessment Schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 8.6.1).

As per Section 4.5, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits), regular phone or virtual calls can occur (every 12 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-1 Safety Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of otic or oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g. OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Weight	Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 1-1.

8.4.1 Electrocardiograms

The Fridericia QT correction formula (QTcF) must be used for clinical decisions to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single 12 lead ECGs are collected.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs on non-heat-sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings during the study.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.2 Clinical safety laboratory tests

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

In all cases, the Investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits).

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

Special clinical laboratory evaluations

In addition to hematology and clinical chemistry safety laboratory and urinalysis, thyroid-specific assays, endocrine function tests, and coagulation assays will be obtained as per the Table 8-2 below.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are required to allow the determination of the outcome of the event where possible.

Clinically notable laboratory findings are defined in Appendix 3 (Section 10.3).

Table 8-2 Clinical Laboratory Evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology (only to be assessed in case of abnormalities in the full blood count), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
CCI	
Coagulation	Prothrombin Time (PT), International Normalized Ratio (INR), activated Partial Thromboplastin Clotting Time (aPTT)
Liver Event Testing and Liver Follow-Up Testing	Albumin, ALP, ALT, AST, CK, GGT, GLDH, INR, PT, and Total Bilirubin (TBIL). Test for hemolysis (haptoglobin, reticulocytes, unconjugated [indirect] bilirubin).

Test Category	Test Name
	These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring.
Renal follow-up	Tests that may be done in addition to routine testing (i.e. serum chemistry & urinalysis), to be performed in case of follow-up to renal safety events when indicated in Section 10.6, Renal safety monitoring: Urine protein, albumin and creatinine (for urine protein; creatinine ratio (UPCR) and urine albumin; creatinine ratio (UACR)), repeat Serum Creatinine. Repeat standard chemistry testing and standard urinalysis (Microscopic Panel (Casts, Crystals, Bacteria, Epithelial cells, Erythrocytes, Leukocytes) and Macroscopic panel (Dipstick) (Color, Bilirubin, Glucose, Ketones, Leukocytes esterase, Macroscopic Blood, Nitrite Occult Blood, pH, Protein, Specific Gravity, Urobilinogen)), urine sediment & microscopy
Additional tests	NT-proBNP (considered a pharmacodynamic biomarker)
Pregnancy Test	Serum pregnancy test refer to 'Pregnancy testing' in Section 8.4.3

8.4.3 Pregnancy testing

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm while taking drug and for 24 hours after stopping study medication.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

As per Section 4.5, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits), if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.4 Appropriateness of safety measurements

CCI

Cardiac function and status are monitored by efficacy assessments including RHC, echocardiography, and 6MWT which are detailed under the efficacy measures in the study.

Further safety assessments (hematology, serum chemistry, coagulation, ECGs, vital signs, physical exams) are standard for investigations monitoring general safety in Phase 2 clinical trials.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient Reported Outcomes

The participant must be given the PRO measures to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measures.

The site personnel should check PRO measures for completeness and ask the participant to complete any missing responses. The responses either captured on paper, and subsequently entered manually into the eCRF, or stored electronically in the database will be considered the source file.

Completed measures must be reviewed and assessed by the Investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, Investigators should not encourage the participant to change responses reported in the completed questionnaires. Investigators must follow reporting instructions outlined in Section 8.6 of the study protocol.

The two patient reported outcomes utilized in this study are emPHasis-10 and PAH-SYMPACT. EmPHasis-10 is a total of 10 questions on an ordinal scale to determine the impact pulmonary arterial hypertension has on aspects of health-related quality of life. PAH-SYMPACT is a validated PAH-specific scale that monitors participant symptoms and clinical experience that is sensitive to improvement.

The Borg scale being used in conjunction with the 6MWT is also a PRO, but is handled separately, as described in Section 8.3.3.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

8.6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in a participant with the underlying disease.

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

1. SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated Participants: SAEs collected between time participant signs ICF until 30 days after the participant has discontinued from study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable

8.7 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this extension study.

8.8 CCI

CCI [redacted]

CCI

CCI

CCI

CCI

CCI

8.8.1 CCI

CCI

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics OR Medical resource utilization and health economics

Health economics and medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

9.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received. The safety analysis set will include all participants that received any study treatment.

The PD analysis set will include all participants who received study treatment and had no protocol deviations with relevant impact on PD data.

9.2 Statistical analyses

9.2.1 General considerations

The safety analysis set will be used in the analysis of all safety variables.

9.2.2 Participant demographics and other baseline characteristics

Demographic and baseline characteristics of all patients in the extension study will be summarized for the safety population.

9.2.3 Treatments

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. The duration of exposure (in weeks) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary aim of the study is to assess the long-term safety of LTP001 in participants with PAH. Safety assessment will include AEs, SAEs, vital signs, ECGs, and safety laboratory measurements.

9.3.1 Definition of primary endpoint(s)

Adverse events (AEs)

Study emergent AEs in the extension study will be summarized and listed. Also, all study emergent AEs in both the parent study and extension study will be summarized.

Consistent with the parent study CLTP001A12201 definitions, AEs starting after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term will be classified as a treatment emergent AE. The following treatment emergent adverse events summaries will be produced:

- by primary system organ class and preferred term
- by primary system organ class, preferred term and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term.

The number and percentage of participants with adverse events will be summarized.

Vital signs

Vital signs data will be summarized by visit/time.

Electrocardiogram (ECG)

All ECG data, including PR, QRS, QT, QTcF and RR, will be listed by participant and visit/time, and abnormalities will be flagged. Summary statistics will be provided by visit/time. Categorical Analysis of QTcF (Fridericia's formula) interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT or QTc intervals or changes from baseline will be presented. The number and percentage of participants with clinical notable QTcF will be summarized.

Laboratory data

All laboratory data will be listed by participant and visit/time, and abnormalities will be flagged if normal ranges are available. Summary statistics will be provided for each lab parameter at each visit.

9.3.2 Statistical model, hypothesis, and method of analysis

The long-term safety of LTP001 will be evaluated in this extension study.

All analyses will be based on frequency counts and summary statistics. No statistical models will be used.

The primary analysis population will be the Safety analysis set.

9.3.3 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

9.3.4 Sensitivity analyses

Not applicable

9.3.5 Supplementary analysis

Not applicable

9.4 Secondary endpoint(s)/estimand(s) analysis

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

Change from baseline for efficacy endpoints including the right heart catheterization (RHC) parameters, 6-Minute Walk Distance (6MWD), and N-terminal fragment of the prohormone B-type natriuetic peptide (NT-proBNP) will be descriptively summarized by visit/time for treatment group (treatment received in the parent study), and overall. The baseline measurement for the extension will be the baseline measurement taken during the parent study CLTP001A12201. Graphs (e.g., spaghetti plot) will be provided to show individual time courses of parameters for the extension study together with the parent study.

Additionally, changes from baseline for efficacy endpoints will be descriptively summarized by visit/time for treatment group (treatment received in the parent study), and overall using a different baseline strategy: participants receiving LTP001 in the parent study will use the baseline of parent study as the baseline; participants switching from placebo in parent study to LTP001 in extension study will use the baseline of extension study as the baseline.

Time to clinical worsening will be analyzed using survival analysis (i.e., Kaplan-Meier) and the corresponding 80% confidence interval will be computed using the appropriate method.

9.4.2 Safety endpoints

Refer to Section 9.3.1.

9.4.3 Patient reported outcomes

PROs (emPHasis-10 and PAH-SYMPACT scores) will be summarized as the original scores, as well as change from baseline, by time/visit. The baseline measurement for the extension study will be the baseline measurement of the parent study CLTP001A12201. Missing data may be imputed using a last observation carried forward approach (LOCF) as necessary.

9.5 Exploratory endpoint(s)/estimand(s) analysis

9.5.1 CCI

CCI

9.5.2 CCI

9.6 (Other) Safety analyses

Not applicable

9.7 Other analyses

Not applicable

9.8 Interim analysis

Not applicable

9.9 Sample size determination

Not applicable

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC , US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form (ICF).

A copy of the ICF(s) must be provided to the participant.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - [redacted]

- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Patient information sheet for female partners of any male participants who took study treatment

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

For the development of LTP001 in pulmonary arterial hypertension, with the start of the parent study, a DMC has been established.

10.1.4.1 Data Monitoring Committee

The parent study to this extension study will include a Data Monitoring Committee (DMC). The DMC will assess at defined intervals the progress of the clinical trial, safety data, and critical efficacy variables and recommend to Novartis whether to continue, modify, or terminate the trial and program. The DMC will be in place at least until the parent study is completed.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations are described in a separate charter that is established between Novartis and the DMC.

10.1.5 Data collection and database management

10.1.5.1 Data collection for off-site procedures

All data captured for this study will have an external originating source (either written or electronic) with the Case Report Form (CRF) not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated Investigator staff will enter the data required by the protocol into the Electronic CRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.1.1 Data collection for off-site procedures

The OHPs will enter data at off-site visits into electronic source documentation forms contained in an eSource Direct Data Capture (DDC) platform, which has been validated for use in clinical research. Where paper source documentation exists, images of documentation will be uploaded electronically into the same platform as certified copies, and the original documentation will then be sent to the investigator.

Data contained in the platform are available to site and sponsor staff based on role-based access and permissions and will be stored in a robust and secure cloud-based back-end environment. Only sponsor staff who are responsible for field monitoring activities will have access to the source data, which may include some personally identifiable information, consistent with the access that is provided to a field monitor in a traditional onsite clinical trial model.

Relevant data in the eSource DDC platform may be manually transcribed by site staff into the study EDC system. Alternatively, the platform allows for configuration that enables data to be automatically exported into the study EDC system.

Certified copies of data in the eSource DDC platform will be provided to investigator and/or site personnel, and promptly and regularly uploaded into the participant's medical records, according to local guidelines.

Investigators will have continuous, near real time access to this study and all participant records within this study in the eSource DDC platform, with the ability to add, edit, review and sign forms within participant records.

The platform maintains a secure, GCP-compliant audit trail and uses measures such as encryption and access controls to ensure that data privacy and security is maintained.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Baseline and study completion dates, as well as data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis / CRA organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

This is required in order to meet the EU Clinical Trial Regulation 536/2014, which is effective January 2022 for new protocols.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it

to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
bid	Twice a Day
BMP	Bone Morphogenic Protein
BMPR2	Bone Morphogenetic Protein Receptor type II
BUN	Blood Urea Nitrogen
CCI	[redacted]
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Cardiac Output
CO_2	Carbon Dioxide
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
CCI	[redacted]
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ERA	Endothelin-Receptor Antagonist
eSource	Electronic Source
FIH	First in Human
CCI	[redacted]
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
hCG	Human Chorionic Gonadotrophin
HR	Heart Rate
I.V.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
CCI	[redacted]
LLN	Lower Limit of Normal
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
mPAP	mean Pulmonary Arterial Pressure
ng	Nanogram(s)
NT-proBNP	N-terminal fragment of the prohormone B-type Natriuetic Peptide
NYHA	New York Heart Association
OHP	Off-site HealthCare Professional
OLE	Open Label Extension
p.o.	Oral(ly)
PA	PosteroAnterior
PAH	Pulmonary Arterial Hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic(s)
PDE5i	Phosphodiesterase type 5 inhibitors
PRO	Patient Reported Outcomes
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
PT	Prothrombin Time
PVR	Pulmonary Vascular Resistence
qd	Once a Day
QTcF	QT interval corrected by Fridericia's formula
RA	Right Atrium
RVFAC	Right Ventricular Fractional Area Change
s.c.	SubCutaneous
SAE	Serious Adverse Event
SD	Standard Deviation
sGC	soluble Guanylate Cyclase
SMURF1	SMAD-specific E3 Ubiquitin Protein Ligase 1
SoA	Schedule of Activities

SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TASV	Tricuspid Annular Systolic Velocity
TGF-beta	Transforming Growth Factor beta
TLC	Total Lung Capacity
TTCW	Time to Clinical Worsening
ULN	Upper Limit of Normal
WHO	World Health Organization
WoC	Withdrawal of Consent

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants

eSource Direct Data Capture (DDC)	eSource DDC refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Hybrid Trial Design	A trial model incorporating both onsite (traditional site based) and offsite (decentralized) elements within the same study design.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site Healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location

Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Telemedicine	Electronic information and telecommunications technologies (both video-based and audio-only) to facilitate the delivery of health care and health related education where participant and Investigator and site personnel are not in the same location.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

10.3 Appendix 3: ECG values and vital signs

10.3.1 Clinically notable laboratory values and vital signs

The following clinically notable laboratory values need to be noted and their clinical significance in light of the underlying PAH condition needs to be considered (does condition cause symptoms; is condition a sign for disease progression; is condition a potential side effect of LTP001 or other PAH directed therapy?)

Clinically Notable Laboratory Values:

Systolic blood pressure > 165 mm Hg or < 80 mm Hg in absence of arterial hyper- or hypotension at baseline

Diastolic blood pressure > 109 mm Hg or < 50 mm Hg in absence of arterial hyper- or hypotension at baseline

Pulse rate > 99 bpm or < 50 bpm and change by 20 bpm or more from baseline

QTcF increase by > 60 ms

All QTcF > 500 ms

QTcF > 480 ms if normal at study entry

QRS-Duration > 120 ms when normal prior to study enrolment.

PR - value > 220 ms when normal at prior to study enrolment

AV-block > Grade 2a

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time-points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-1 in Appendix 5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Since deterioration of PAH may result in increases of liver values it should be checked if an increase of liver values might be secondary to a deterioration of right heart failure. Liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation. Increased liver values considered secondary to deterioration of right heart function are not considered liver events

- Liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 7.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include, as per the investigator's discretion to allow for a causality assessment: serology tests, imaging and pathology assessments, hepatologist’s consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Notify Novartis study lead and medical lead of any finding of a liver event identified not explained by PAH worsening for further follow-up assessments.

Table 10-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.

	ALT	TBL	Liver Symptoms	Action
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

10.6 Appendix 6: Renal safety monitoring

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Renal safety parameters will be checked at all visits. Careful monitoring of deterioration of renal function or of pathologic changes in the urinalysis is required. The below definitions mandate to classify a renal parameter deviation as a renal event.

Table 10-4 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase > 25% fold compared to baseline	Follow up within 1-2 days (Refer to Table 8-2)
Urine Event	
New onset dipstick proteinuria ≥3+ OR New onset dipstick hematuria ≥3+ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)	Follow up within 2-5 days (Refer to Table 8-2)
For all renal events:	
Document contributing factors in the eCRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor subject regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 20% of baseline or	
Event stabilization: sCr level with ±20% variability over last 2 months	
Further recommendations on the follow-up for renal events can be found in the investigator portal (Follow-up for renal events document).	

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References are available upon request

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