NOVARTIS

Novartis Research and Development

LTP001

Clinical Trial Protocol CLTP001A12201 / NCT05135000

A randomized, participant- and investigator-blinded, placebo-controlled study to investigate efficacy, safety and tolerability of LTP001 in participants with pulmonary arterial hypertension

Document type:	Amended Protocol Version
EUDRACT number:	2021-000670-28
Version number:	03 (Clean)
Clinical Trial Phase:	IIa
Release date:	01-Nov-2022

Table of contents

List of tables

List of figures

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
ATS	American Thoracic Society
AUC	Area Under the Curve
bid	Twice daily
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
COA	Clinical Outcome Assessment
CCI	[redacted]
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTT	Clinical Trial Team
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
ERA	Endothelin Receptor Antagonist
ERS	European Respiratory Society
eSource	Electronic Source
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the first second
CCI	[redacted]
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
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
ID-1	Inhibitor of differentiation/DNA binding
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]
LLOQ	Lower Limit of Quantification
LVEDP	Left Ventricular End Diastolic Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
mPAP	mean Pulmonary Arterial Pressure
NT-proBNP	N-terminal fragment of the prohormone B-type Natriuretic Peptide
NYHA	New York Heart Association
OHP	Off-site Healthcare Professional
OLE	Open Label Extension
p.o.	oral(ly)
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic(s)
PDE5i	Phosphodiesterase type 5 inhibitors
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient Reported Outcomes
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
PT	prothrombin time
PVR	Pulmonary Vascular Resistance
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RA	Right Atrium

RVFAC	Right Ventricular Fractional Area Change
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
sGC	Soluble guanylate cyclase
SoC	Standard of Care
SMURF1	SMAD-specific E3 ubiquitin protein ligase 1
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

Glossary of terms

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.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
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 (CCI [redacted])
Electronic Data Capture (EDC)	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
Electronic Source Direct Data Capture (eSource DDC)	Any technology that allows the capture of clinical study source data electronically by the investigator or site staff at the point of care, into an electronic form that has been validated to capture clinical data.
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
Estimand	As defined in the ICH E9 (R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as

	the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Hybrid Trial Design	A trial model incorporating both onsite (traditional site based) and offsite (decentralized) elements within the same study design.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Participants who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
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)
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.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
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.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
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.

Amendment 03 (01-Nov-2022)

Amendment rationale

The primary purpose of this amendment is to incorporate [redacted].

Exclusion criterion 11 has been updated with information about sperm donation to reflect the requirements described in Section 8.4.3[1].

The protocol appendix was updated with further guidance details for hepatic and renal alert criteria and event follow-up.

In addition, Section 6.2 has been updated with considerations about the use of LTP001 in combination with allowed standard therapies[1].

This amendment also corrects for administrative inconsistencies and adds further protocol clarifications to ensure data quality[1].

[redacted]

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 approval 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.

Amendment 02 (March 2022)

The primary purpose of this amendment is to correct errors in the assessment schedule. In addition, further clarifications are made in the text, as follows:

- Updated clinical safety data
- Added guidance text for Six Minute Walk Test (6MWT) and CCI
- Updated withdrawal of consent language to improve clarity

Amendment rationale

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

At the time of this amendment, the study has not achieved first patient first visit.

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 approval 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.

Amendment 01 (December 2021)

Amendment rationale

The primary purpose of this amendment serves to address feedback received by Novartis for the study protocol:

- A requirement of a negative serum pregnancy test within 7 days prior to first dose administration on Day 1 to rule out pregnancy where required by health authority (CCI or local regulations. In countries where this is not required a negative urine pregnancy test needs to be available prior to dosing on Day 1.
- Excluding participants who CCI
- Excluding participants who have a long QT syndrome or who take drugs that are known to prolong the QT interval.
- CCI
- In addition, the Six-Minute Walk Test (6MWT) is to only be conducted on-site to remove testing variability in the assessment. The requirement for the participant to record IMP dosing every day in the eDiary is removed to decrease the daily burden on participants. Compliance for IMP administration will be done by medication reconciliation. Coagulation assays (PT, INR, aPTT) and CCI were added to the safety laboratory panel.

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

At the time of this amendment, the study has not achieved first patient first visit.

CCI

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 approval 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.

Protocol summary

Protocol number	CLTP001A12201
Full Title	A randomized, participant- and investigator-blinded, placebo-controlled study to investigate efficacy, safety and tolerability of LTP001 in participants with pulmonary arterial hypertension
Brief title	Study of efficacy and safety of LTP001 in pulmonary arterial hypertension participants
Sponsor and Clinical Phase	Novartis Phase IIa
Investigation type	Drug
Study type	Interventional
Purpose and rationale	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.
Primary Objective(s)	The primary objective of this study is to assess the change in pulmonary vascular resistance (PVR) at Week 25 in participants treated with LTP001 compared to placebo.

Secondary Objectives	• To evaluate the effect of LTP001 on:
	  • Six Minute Walk Distance (6MWD)
	  • Hemodynamic parameters other than PVR
	  • Measurements of right ventricular function
	• To assess the impact of LTP001 on:
	  • Patient Reported Outcomes (PRO).
	  • Time to Clinical Worsening (TTCW)
	  • The N-terminal fragment of the prohormone B-type Natriuetic Peptide (NT-proBNP)
	• To assess the safety and tolerability of LTP001
	• To investigate the pharmacokinetics (PK) of LTP001

Study design	This is a non-confirmatory, randomized, subject- and investigator-blinded, placebo controlled study of LTP001 in PAH participants. 44 participants will be randomized in a 3:1 ratio of LTP001 [redacted] mg to placebo. Participants will be screened for up to 8 weeks followed by 24 weeks of daily dosing with visits approximately every 4 weeks. One follow up visit will also be the end of study visit and occurs approximately 30 days after the end of treatment. Total study duration is approximately 37 weeks from start of screening to end of study visit. If a participant continues into the open-label extension study, then the follow-up visit may be skipped.
Study population	The study population is comprised of male and female adults with PAH. A total of approximately 44 participants are planned to be enrolled and randomized with approximately 40 participants available for the primary endpoint analysis.
Key Inclusion Criteria	• History of PAH belonging to one of the following subgroups of the World Health Organization (WHO) Clinical Classification Group 1:

	• Participants with idiopathic pulmonary arterial hypertension (IPAH) • Hereditary pulmonary arterial hypertension • Congenital heart disease (surgically repaired at least 12 months prior to screening) • Drug or toxin induced (for example, anorexigen, or methamphetamine use). • Resting mean pulmonary arterial pressure (mPAP) > 25 mmHg; pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) < 15 mmHg, as determined by right heart catheterization (RHC) within 20 days of randomization. • Pulmonary Vascular Resistance (PVR) > 6 Wood units (480 dynes s/cm^5), as determined by right heart catheterization within 20 days of randomization. • WHO Functional Class II-III • 6MWD must be between 150 and 550 m (inclusive). The qualifying test needs to be within 20 days of randomization. To meet the above criterion additional six minute walk test (6MWT) may be performed up to a maximum of 3 tests in total prior to dosing; the minimal time difference between two tests should be at least 4 h. • Standard of care therapy which is stable at least 6 weeks prior to RHC and qualifying 6MWT assessment within 20 days of randomization. Standard of care includes one or more of the following treatments: • prostacyclin analogues and receptor agonists (if I.V., dose adjustments must be within 20% of initial stable dose) • endothelin receptor antagonists (ERAs) • phosphodiesterase type 5 inhibitors (PDE5i) • soluble guanylate cyclase (sGC) stimulators
Key Exclusion criteria	• Participants with pulmonary hypertension (PH) in the WHO Clinical Classification Groups 2-5, and any PAH Group 1 subgroups not covered by Inclusion Criterion #4. • Participants with a history of left sided heart disease, chronic left sided heart failure, congenital or acquired valvular disease compromising left ventricular function and/or pulmonary venous hypertension or symptomatic coronary disease (non-symptomatic, re-vascularized coronary artery disease would be acceptable)). • Participants with obstructive lung disease defined as: FEV1 / FVC < 60% and FEV1 < 60% of predicted value after bronchodilator administration as well as participants with moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value. Testing must have occurred within 24months of screening. If historical testing is not available, then lung function testing must be conducted during the screening period. • Acute or chronic impairment (other than dyspnea), which would limit the ability to comply with study requirements, including interference with physical activity and execution of study procedures such as 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, multiple sclerosis, need for walking aids).

Study treatment	Active treatment: LTP001 administered as [redacted] mg once daily [redacted] (as [redacted] containing LTP001 [redacted] mg plus [redacted] containing LTP001 [redacted] mg) Placebo to LTP001 administered once daily [redacted] (as [redacted] containing the placebo to LTP001 [redacted] mg and [redacted] containing the placebo to LTP001 [redacted] mg)
Treatment of interest	The randomized treatment LTP001 [redacted] mg daily or placebo on top of allowed standard of care treatment for PAH. The dose of the allowed concomitant medication should remain stable during the trial.
Efficacy assessments	• Right heart catheterization (assessment of PVR, CO, right ventricular and pulmonary artery pressures) • Echocardiography • 6MWD • Clinical worsening criteria
Pharmacodynamic assessments	• N-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP)
Pharmacokinetic assessments	• Drug concentrations of LTP001 at defined timepoints
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory markers in blood and urine, ECGs and vital signs. Monitoring of cardiac function is defined as part of the efficacy assessments (Echocardiography, 6MWT, clinical worsening).
Other assessments	• [redacted] • [redacted] • [redacted] • Patient Reported Outcomes (emPHasis-10 and PAH-SYMPACT)
Data analysis	The purpose of this study is to determine whether WHO Group 1 PAH participants who belong to WHO Functional Class II-III would benefit with LTP001 as compared to placebo, while both arms receive standard of care (stable on a combination or single therapeutic from the following: ERA, PDE5i, sGC stimulators, prostacyclin analogues and receptor agonists (if I.V., dose adjustments must be within 20% of initial stable dose). The primary endpoint of interest is PVR and the primary analysis is change from baseline in PVR at Week 25 based on approximately 40 participants (3:1 randomization). Within a Bayesian analysis framework approximately 8 patients will be borrowed by setting up a weakly informative prior from historical studies on SoC for the placebo group. An interim analysis is planned after 20 participants complete Week 25 to assess futility. Change from baseline or fold change as appropriate for the PVR will be summarized. Other secondary endpoints relevant to efficacy, PK and safety will be summarized descriptively.
Key words	Pulmonary arterial hypertension, pulmonary vascular resistance, 6 minute walk distance, time to clinical worsening, SMURF1 inhibitor, echocardiography, patient reported outcomes

1 Introduction

1.1 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, endothelin receptor antagonists, soluble guanylate cyclase stimulators and prostacyclin analogues and receptor agonists), are leaving 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 study of LTP001, healthy participants completed dosing with single doses of LTP001 CCI [redacted].

Overall, all doses were well tolerated. For further details, refer to Section 4.5 and the Investigator's Brochure. There was no dose-dependency in the frequency of AEs. AEs were less frequent in the treatment arm than in the placebo arm. There were no serious or severe AEs. There were no significant findings when ECGs, clinical laboratory assessments and vital signs were reviewed.

In the multiple dose part there was no dose-dependency in the frequency of AEs. CCI [redacted]

CCI [redacted] There were no other significant findings when ECGs, clinical laboratory assessments and vital signs were reviewed.

For further information please refer to the Investigator`s Brochure.

CCI [redacted]

CCI [redacted]

[redacted]

1.2 Purpose

The purpose of this study is to explore the efficacy and safety of LTP001 in participants with WHO Group 1 pulmonary hypertension (PH), also referred to as Pulmonary Arterial Hypertension (PAH).

This proof of concept study will be executed as the efficacy of SMURF1 inhibition has not yet been established in the PAH population. This study will provide insights to whether SMURF1 inhibition is effective in reducing the pulmonary vascular resistance, improves patient symptom burden and increases the time to clinical worsening. These endpoints are considered relevant for the characterization of the disease progression in PAH. CCI [redacted]

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of LTP001 in participants with pulmonary arterial hypertension (PAH).	• Change from baseline right heart catheterization PVR at Week 25
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of LTP001 on Six Minute Walk Distance (6MWD)	• Change from baseline in 6MWD at Weeks 13 and 25
• To evaluate the effect of LTP001 on hemodynamic parameters other than PVR	• Right heart catheterization assessments including RV pressures, pulmonary artery pressures, wedge pressure, and cardiac output at Week 25
• To assess the effect of LTP001 on measurements of right ventricular function	• Change from baseline in tricuspid annular plane systolic excursion (TAPSE) by echocardiography at Weeks 5, 13, and 25 Change from baseline in tricuspid annular systolic velocity (TASV) by echocardiography at Weeks 5, 13, and 25 Change from baseline of peak velocity of excursion (RV S') by echocardiography at Weeks 5, 13, and 25 Change from baseline in fractional area change (FAC) by echocardiography at Weeks 5, 13, and 25
• To assess the impact of LTP001 on patient reported outcomes (PRO)	• Change from baseline in EmPHasis-10 and PAH-SYMPACT at Weeks 13 and 25
• To assess the safety and tolerability of LTP001.	• AEs, SAEs, vital signs, ECGs, safety laboratory measurements

• To assess the impact of LTP001 on Time to Clinical Worsening (TTCW).	• Time to any of the following:
	  • 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

Objective(s)	Endpoint(s)
	• 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 investigate the pharmacokinetics (PK) of LTP001	• Cmax and tmax (Day 1 and Week 25)
• 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	

2.1 Primary estimands

Not applicable.

2.2 Secondary estimands

Not applicable.

3 Study design

This is a randomized, participant- and investigator-blinded, placebo-controlled, parallel group study of LTP001 or placebo on top of standard of care in participants with PAH.

Standard of care includes one or more of the following treatments: prostacyclin analogues or receptor agonists (if I.V., dose adjustments must be within 20% of initial stable dose), endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and soluble guanylate cyclase stimulators.

Figure 3-1 Study Design

A screening period of 8 weeks will be used to assess eligibility prior to randomization. Screening procedures can occur throughout the 8 week screening period, except for those procedures which are defined at specific time-points such as the right heart catheterization, qualifying 6MWT, PROs, and CCI in the Assessment Schedule (Table 8-1). In particular, the screening period may be used to assess if a participant appears to be adequately stable on current therapy and that the criteria for allowed concomitant medication is adhered to for the time period defined in Section 6.2.1 and Section 5.1 prior to pre-dose qualifying 6MWD and the baseline right heart catheterization. Participants who fulfill all enrollment criteria earlier may have a shorter screening period.

Preference is for screening procedures to occur from least invasive to most invasive (echocardiography, right heart catheterization). Since laboratory measurements require central review, laboratory assessments should occur 15 or more business days prior to planned randomization. The right heart catheterization and the qualifying 6 minute walk test prior to first dose should occur within 20 days prior to randomization/planned first dose. Note, the RHC and qualifying 6MWT may be performed on the first dosing day if they are completed prior to randomization. During screening, participants will be given guidance on how to use the wearable device (if they have chosen to use it), which will be provided approximately 7 days prior to scheduled start of dosing. On Day 1, eligible participants will be randomized to one of two treatment arms. Approximately 44 participants with PAH will be randomized in a 3:1 ratio to either oral LTP001 or placebo daily for 24 weeks.

During the treatment period, visits will occur approximately every 4 weeks for assessments of efficacy and safety as per the assessment schedule (see Table 8-1). Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), and adverse event and serious adverse event monitoring. Right heart catheterization to measure PVR for the primary objective and primary efficacy endpoint is performed at the end of the treatment period on Day 169 (Week 25). Other measures of efficacy include echocardiography (Week 5, Week 13, and Week 25) and the 6MWT (Week 5, Week 13, and Week 25). 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 the following visits: Day 1, Week 5, Week 9, Week 13, Week 17, Week 21, and Week 25. CCI

Following the end of the treatment period, participants will have one follow-up visit approximately 30 days after end of treatment (Week 29), which will serve as the End of Study (EOS) visit. All visits from Week 5 to Week 25 have a plus 5 day visit window and Week 29 has a plus or minus 5 day visit window. If treatment is ended early for any reason, the end of treatment visit procedures should occur as soon as possible thereafter.

An unblinded interim analysis (IA) is planned for when approximately 20 participants complete the 24-week treatment period, and may include analyses to assess sample size, efficacy, PK, PD, or safety. The analysis may be used for internal decision making of the further development of LTP001 in PAH patients. Further analyses will be prepared for review by the DMC per the DMC charter.

Pending the safety and efficacy profile of LTP001 that is observed in the current study (absence of study treatment discontinuation criteria or study stopping rules or an emerging safety concern in the review of the data), participation in the open label extension study may be offered to participants once the extension study is approved by the competent authorities and review boards.

Transition from the current study in an open label extension (OLE) study will be defined in the separate protocol. For participants enrolling into the OLE study, the EOS visit will be skipped in order to continue treatment in the OLE protocol. Replacement of such procedures done at the EOS will be defined in the OLE study protocol.

3.1 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 at an off-site location, as defined in Table 8-1. 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-patient shipment of study supplies
- Direct-to-patient shipment of study treatment (refer to Section 6)
- Electronic Source (eSource) Direct Data Capture (DDC)

Procedures for off-site visits utilizing the above listed elements are further detailed in the Science 37 Operational Manual and Nursing Manual of Operations and Procedures.

3.1.1 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 (including, but 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

3.1.2 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.

3.1.3 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 video conferencing which allows the patient, 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 11.1.1)

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall (parallel design)	Parallel group design is the most efficient in studies with treatment duration of 6 months
Randomization (strata, allocation ratio)	Weighted 3:1 randomization increasing the number of participants on LTP001 thus maximizing the clinical information on LTP001 in the PAH population
Blinding	Participant- and investigator-blinding are required to avoid bias on study outcomes by knowing the treatment arm
Duration of 24-week treatment period	At earlier time points, the primary endpoint (change from baseline in PVR) may not have achieved the maximal effect, as remodeling is considered a slow process and may take time to reverse. Duration of treatment provides also evidence that effect is sustained over 6 months.
Interim analysis when approximately 20 participants completed Week 25	Allows for early decision on program or study continuation or discontinuation
CCI	

CCI	
Aged up to 75 years old	CCI Participants up to age 75 are included in the study as this age range is expected to be representative of the patient population.
Safety Monitoring	Regular collection of ECGs, vital signs, clinical laboratory assessments, and body weight will be undertaken at visits approximately every 4 weeks during treatment. Cardiac function will be additionally monitored by echocardiography. CCI A DMC will review the study data at defined time points specified in the DMC charter.
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

4.1.1 Rationale for choice of background therapy

The background therapy will be the previously used therapy by the participant. PAH-directed maintenance therapy needs to be tolerated and kept stable for 6 weeks prior to the RHC and 6MWT assessments preceding randomization, but diuretic therapy may be adjusted if needed (for details please refer to Section 6.2.1). Otherwise, the background therapy should not be changed during the study. 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 9.1) and subsequently return for the End of Treatment assessments.

4.2 Rationale for dose/regimen and duration of treatment

LTP001 will be administered once daily CCI at a dose level of CCI mg.

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

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

Placebo will be used as a comparator to LTP001 to provide an unbiased control for assessing and interpreting safety data as well as clinical efficacy data generated from participants exposed to LTP001.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis is planned after approximately 20 participants complete the treatment period (Week 25). For these participants, the primary endpoint, PVR, will be considered for non-binding futility and further evaluation of the totality of the data (safety, PK/PD, and other clinical endpoints along with PVR) will be considered for preliminary efficacy. PVR variability will also be evaluated during this interim for sample size re-estimation as appropriate.

Analyses for DMC review will be conducted as defined in the DMC charter. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor’s clinical development projects in general, or in case of any safety concerns. Blinded trial safety data will be reviewed on an ongoing basis (at least every month). Pathway and target engagement markers may be analyzed at additional time-points to gain early insights to which degree they are modulated and to allow adjustments on the selection of markers (e. g. dropping markers less sensitive then others; widening panel to further markers).

Additional information is presented in the interim analysis section (see Section 12.7).

4.5 Risks and benefits

Potential risks are based on the mechanism of action, the nonclinical toxicology data and the safety data from the first in human 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

Clinical data

Single doses of LTP001 CCI were well tolerated and did not show safety signals for LTP001 in the first in human study. Adverse events under LTP001 in the single dose cohorts were abdominal pain, blood testosterone increased, diarrhea, sinus congestion and skin lesion. All AEs were mild or moderate and resolved without pharmacological intervention.

Multiple doses of LTP001 CCI were well tolerated. CCI

CCI [redacted]

CCI [redacted]

Apart from the mentioned events, across participants, clinical laboratory assessments, ECGs, and vital signs did not show significant abnormalities. CCI [redacted]

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. But, 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, which is the primary efficacy assessment and is performed at screening (up to Day 1) and at the end of treatment.

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.

Other procedures in the study are non-invasive. 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.

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, LTP001 has not been used outside a Phase I study in healthy volunteers, thus, efficacy has not been proven and there is no proven direct medical benefit for participants in this study. There is also no other SMURF1 inhibitor drug tested in clinical studies. Participants randomized to the LTP001 treatment arm may benefit in the current study if LTP001 proves to be safe and effective.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 34 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 8-1).

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.

See the Section 8.5.3.2 on the potential use of residual samples.

4.5.2 Risks and benefits of off-site visits

Participants are not anticipated to be exposed to greater risks when participating in off-site assessments. OHPs will perform assessments according to the same processes and instructions defined in the protocol and study manuals for onsite visits, thus data integrity is also expected to be comparable to onsite assessments. Safety management in an off-site setting will adhere to the same quality standards as for the traditional onsite model and remains under the responsibility of the investigator (refer to Section 3.1.1).

4.6 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 onsite 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.

5 Study Population

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

Approximately 44 participants will be randomized in the study. Approximately 40 participants are expected to complete the 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 patients.

Participant selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation.

Deviation from **any** entry criterion excludes a participant from enrollment into the study. Details on re-screening are located in Section 8.1.

5.1 Inclusion criteria

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

1. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
2. Written informed consent must be obtained before any assessment is performed.

3. Male and female patients ≥ 18 and ≤ 75 years of age on the day of Informed Consent signature.
4. History of PAH belonging to one of the following subgroups of the World Health Organization (WHO) Clinical Classification Group 1:
   - Patients with idiopathic pulmonary arterial hypertension (IPAH)
   - Hereditary pulmonary arterial hypertension
   - Congenital heart disease (surgically repaired at least 12 months prior to screening)
   - Drug or toxin induced (for example, anorexigen use, or methamphetamine use).

   5. Resting mean pulmonary arterial pressure (mPAP) > 25 mmHg; pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) < 15 mmHg, as determined by right heart catheterization within 20 days of randomization.
6. Pulmonary Vascular Resistance (PVR) > 6 Wood Units (WU) corresponding to 480 dynes s/cm^5, as determined by right heart catheterization (RHC) within 20 days of randomization.
7. WHO Functional Class II-III
8. At least one 6MWT distance must be between 150 and 550 m (inclusive). The qualifying test needs to be within 20 days of randomization. To meet the above criterion additional 6MWT may be performed up to a maximum of 3 tests in total prior to dosing; the minimal time difference between two tests should be at least 4 h.
9. Standard of care therapy which is stable at least 6 weeks prior to baseline RHC and qualifying 6MWT at screening (and up to Day 1 pre-dose). Standard of care includes one or more of the following treatments:
   - prostacyclin analogues and receptor agonists
   - endothelin receptor antagonists
   - phosphodiesterase type 5 inhibitors
   - soluble guanylate cyclase stimulators

5.2 Exclusion criteria

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

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or excipients
3. Patients with pulmonary hypertension (PH) in the WHO Clinical Classification Groups 2-5, and any PAH Group 1 subgroups that were not covered by Inclusion Criterion #4.
4. Participants with a history of left sided heart disease, chronic left sided heart failure, congenital or acquired valvular disease compromising left ventricular function and/or pulmonary venous hypertension or symptomatic coronary disease (asymptomatic, revascularized coronary artery disease would be allowed).

5. Patients with obstructive lung disease defined as: FEV1/FVC < 60% and FEV1 < 60% of predicted value after bronchodilator administration as well as patients with moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value. Testing must have occurred within 24 months of screening. If historical testing is not available, then lung function testing must be conducted during the screening period.
6. Acute or chronic impairment (other than dyspnea), which would limit the ability to comply with study requirements, including interference with physical activity; execution of study procedures such as 6MWT (e.g., angina pectoris, claudication, musculoskeletal disorder, multiple sclerosis, need for walking aids).
7. Any surgical or medical condition which, in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study. The investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:
   - Moderate or severe hepatic failure (Child-Pugh classification stage B or C)
   - Significant renal impairment with an estimated creatinine clearance < 30 mL/min as calculated by the CKD-EPI formula
8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. 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 End of Study visit (30 days 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.

10. 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.
11. 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. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time specified above.
12. Recently conducted (the program should have been completed at least 8 weeks prior to screening) or planned cardio-pulmonary rehabilitation program based on exercise training during the conduct of the study.
13. Required or planned transplant or heart/lung surgery.
14. CCI [redacted].
15. Any of the following:
    - Known family history of long QT syndrome
    - Known presence of long QT syndrome
    - Current use of any medications which prolong the QT interval
16. CCI [redacted]

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in Section 6.3.

Refer to the ‘Dietary restrictions and smoking’ section (See Section 6.2.4.1) for details of dosing and food intake.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LTP001 [redacted] mg	[redacted]	Oral Use	Double-blind, patient-specific kits	Global
LTP001 [redacted] mg		Oral Use	Double-blind, patient-specific kits	Global
Placebo to LTP001 [redacted] mg		Oral Use	Double-blind, patient-specific kits	Global
Placebo to LTP001 [redacted] mg		Oral Use	Double-blind, patient-specific kits	Global

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants will be assigned on study Day 1 to one of the following two treatment arms/groups in a ratio of 3:1:

LTP001 [redacted] mg administered [redacted] ([redacted]) or placebo to LTP001 ([redacted] administered [redacted].

6.1.4 Post Trial Access

An open label extension (OLE) study is prepared and patients will be offered to participate if in the current study there is no emerging safety concern (safety signal or signal of clinical worsening of PAH more than under placebo). Further details of post trial access will be detailed in the corresponding OLE study protocol.

For participants who enroll in the OLE study, Week 29 (EOS visit) should be skipped.

6.2 Other treatment(s)

6.2.1 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 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.

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

CCI

CCI

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Endothelin receptor antagonists, prostacyclin analogues and receptor agonists, soluble guanylate cyclase stimulators and/or phosphodiesterase type 5 inhibitors for PAH treatment are allowed if participants have been on a stable dose for at least 6 weeks prior to the baseline Right Heart Catheterization and the last 6MWT prior to randomization. The dose(s) should remain unchanged during the study.

- Treatment with diuretics is allowed and may be adjusted during the study within the following limits:
  - No other diuretic is added
  - No parenteral diuretic is added
  - The oral diuretic dose will not increase more than double from initial stable dose level prior to the first dose and will not be changed within 7 days prior to a RHC assessment (if dose adjustment is required, consider to reschedule RHC visit).
- Single administration of medication for diagnostic purposes (such as use for acute vasodilator testing during the RHC procedure) is allowed.
- IV prostacyclin analogues daily dose no more than 20% change from initial stable dose level as determined at the time of screening.

6.2.2 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, ERA, and sGC stimulators, refer to Section 6.2.1) should be kept stable during the study. Note that a required change in PAH-directed therapy due to clinical worsening of PAH should result in treatment discontinuation and appropriate management of the participant with the PAH directed therapy as per the investigators discretion and the participant's need.

In terms of treatments required for other conditions or adverse events, there are no known drug interaction signals with LTP001 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

Table 6-2 CCI

CCI

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

6.2.3 Rescue medication

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 (see Section 9.1.1). 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 6.2.1.

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

6.2.4 Restriction for study participants

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

6.2.4.1 Dietary restrictions and smoking

1. Participants should be encouraged to maintain a healthy diet and abstain from the use of alcohol or (recreational) drugs. Smoking status will be collected as part of the participant demographics.
2. CCI [redacted]

6.2.4.2 Other restrictions

No significant change in physical exercise program from the beginning of the study until after the Week 27 visit.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (See Section 6.1.1).

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 120 day supply. In this case, regular contacts (every 4 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.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 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 each visit during the treatment period 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.

6.3.1.2 Handling of other treatment

It should be checked at each visit if other concomitant PAH specific therapy has been kept stable as specified in the study eligibility criteria (Section 5) and in Section 6.2.1.

6.3.2 Instruction for prescribing and taking study treatment

LTP001 should be taken daily at approximately the same time each day CCI [redacted]. On clinic visit days, the participant should take LTP001 during the clinic visit prior to post-dose PK samples (when applicable), when instructed by the study staff. 6MWT and RHC assessments should be executed at approximately the same time after drug administration each time (+/- 1 hour).

CCI [redacted]

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.

For visit days, the dose administered on the day of PK sample collection to the participant will be recorded on the Dosage Form eCRF. For visits without PK samples, 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 who receive a dose of study medication (LTP001 or placebo), which will state that the participant is participating in a clinical study and may have received an investigational product. This participant study card will also include the contact information of the Study Doctor/Investigative Site. Designated study staff 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.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center 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.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

On study Day 1, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.5 Treatment blinding

Participants, investigator staff (including OHPs) , persons performing the assessments, and the Novartis Clinical Trial Team (CTT) will remain blinded to the identity of the treatment from the time of randomization until database lock except for unblindings listed in Table 6-3.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

The DMC members will be un-blinded as per the procedures described in the DMC charter.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock. Randomization codes may be also disclosed to biomarker analysts (concerned with target engagement markers or pathway engagement markers) who also will keep the blind.

The following method will be used to maintain the blind:

- the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

At the time of safety review/interim analysis for efficacy, the Novartis CTT may create and review unblinded interim reports.

Table 6-3 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis & dose escalation**
Participants	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Independent committees used for assessing interim results	B	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI

B Remains blinded

NA Not applicable

UI Allowed to be unblinded on individual patient level

6.6 Dose escalation and dose modification

Investigational dose adjustments and/or interruptions are not permitted.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator/site staff 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 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.

Off-site treatment compliance will be assessed by the OHP and details of which will be shared with the investigator.

6.7.2 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 9.1 should be observed.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

7 Informed consent procedures

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.

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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 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:
  - CCI [redacted]
  - CCI [redacted]
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- CCI [redacted]

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.

CCI [redacted]

CCI [redacted]

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.

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.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

The following visits may be conducted at an off-site location as allowed by local laws and regulations: Visit 120 (Week 9), Visit 140 (Week 17), Visit 150 (Week 21), and Visit 199 (Week 29).

For all visits, assessments may occur throughout the visit window over multiple days, as needed, except where defined. For Day 1 and Week 25 visits with timed PK draws, only PK samples need to be taken post-dose.

On clinic visit days, the participant should take LTP001 during the clinic visit prior to post-dose PK samples (when applicable), when instructed by the study staff. RHC assessments and 6 minute walk test assessments should be executed at approximately the same time after drug administration each time (+/- 1 hour).

Participants who discontinue from study treatment are to return for 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 or withdraw their consent/oppose the use of their data/biological samples 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 event and concomitant medications not previously reported must be recorded on the eCRF.

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.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**															**EOS**
Visit Name	**Screening**[2]	**Treatment**										**EOT**					**EOS**[20]
Visit Numbers[1]	**1**	**100**					**110**	**120**	**130**	**140**	**150**	**160**					**1999**
Days	**-56 to -1**	**1**					**29 +5**	**57 +5**	**85 +5**	**113 +5**	**141 +5**	**169 +5**					**199 ±5**
Weeks	**-8 to -1**	**1**					**5**	**9**	**13**	**17**	**21**	**25**					**29**
Time (post-dose)	**-**	**Predose**	**0min**	**15min**	**45min**	**120min**	**-**	**-**	**-**	**-**	**-**	**-**	**0min**	**15min**	**45min**	**120min**	**-**
Informed consent[21]	X																
Inclusion / Exclusion criteria	X	X															
Demography	X																
Medical history/current medical conditions	X																
Physical Examination	S						S[3]										S[3]
Lung Function Testing	X[4]																
Body Height	X																
Body Weight	X	X					X	X	X	X	X	X					X
Body Temperature	X	X					X	X	X	X	X	X					X
Blood Pressure and Pulse Rate	X	X					X	X	X	X	X	X					X

Period	**Screening**	**Treatment**															**EOS**
Visit Name	**Screening** [2]	**Treatment**										**EOT**					**EOS**[20]
Visit Numbers[1]	**1**	**100**					**110**	**120**	**130**	**140**	**150**	**160**					**1999**
Days	**-56 to -1**	**1**					**29 +5**	**57 +5**	**85 +5**	**113 +5**	**141 +5**	**169 +5**					**199 ±5**
Weeks	**-8 to -1**	**1**					**5**	**9**	**13**	**17**	**21**	**25**					**29**
Time (post-dose)	**-**	**Predose**	**0min**	**15min**	**45min**	**120min**	**-**	**-**	**-**	**-**	**-**	**-**	**0min**	**15min**	**45min**	**120min**	**-**
Electrocardiogram (ECG)	X	X					X	X	X	X	X	X					X
CCI																	
emPHasis-10[8]	X[9]	X[9]					X[9]	X[9]	X[9]	X[9]	X[9]	X[9]					
PAH-SYMPACT[8]	X[9]	X[9]					X[9]	X[9]	X[9]	X[9]	X[9]	X[9]					
Dose administration[11]			X				X	X	X	X	X		X				
Drug dispensation		S					S	S	S	S	S						
Collect study medication/ perform drug accountability[12]							S	S	S	S	S	S					
Pregnancy and assessments of fertility	S	S[13]					S	S	S	S	S	S					S
Hematology	X[14]	X					X	X	X	X	X	X					X
Clinical Chemistry	X[14]	X					X	X	X	X	X	X					X

Period	**Screening**	**Treatment**															**EOS**
Visit Name	**Screening** [2]	**Treatment**										**EOT**					**EOS**[20]
Visit Numbers[1]	**1**	**100**					**110**	**120**	**130**	**140**	**150**	**160**					**1999**
Days	**-56 to -1**	**1**					**29 +5**	**57 +5**	**85 +5**	**113 +5**	**141 +5**	**169 +5**					**199 ±5**
Weeks	**-8 to -1**	**1**					**5**	**9**	**13**	**17**	**21**	**25**					**29**
Time (post-dose)	**-**	**Predose**	**0min**	**15min**	**45min**	**120min**	**-**	**-**	**-**	**-**	**-**	**-**	**0min**	**15min**	**45min**	**120min**	**-**
Coagulation Assays	X[14]	X					X	X	X	X	X	X					X
Urinalysis	X[14]	X					X	X	X	X	X	X					X
NT-proBNP		X					X	X	X	X	X	X					X
[redacted]																	
Right heart catheterization	X[19]											X					

Period	**Screening**	**Treatment**															**EOS**
Visit Name	**Screening** [2]	**Treatment**										**EOT**					**EOS**[20]
Visit Numbers[1]	**1**	**100**					**110**	**120**	**130**	**140**	**150**	**160**					**1999**
Days	**-56 to -1**	**1**					**29 +5**	**57 +5**	**85 +5**	**113 +5**	**141 +5**	**169 +5**					**199 ±5**
Weeks	**-8 to -1**	**1**					**5**	**9**	**13**	**17**	**21**	**25**					**29**
Time (post-dose)	**-**	**Predose**	**0min**	**15min**	**45min**	**120min**	**-**	**-**	**-**	**-**	**-**	**-**	**0min**	**15min**	**45min**	**120min**	**-**
Echocardiogram	X						X		X			X					
6-Minute Walk Test	X[19]						X		X			X					
Concomitant Medications/ Adverse Events	As required																
Serious Adverse Events	X																
Study completion information																	X

[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] All assessments during screening must be done at the clinic site.
[3] Short physical exam may be employed beginning at Week 5, unless complete physical exam is indicated.
[4] Only to be conducted if historical lung function testing within 24 months of screening is not available.
[5] CCI [redacted]
[6] CCI [redacted].
[8] PROs to be completed by participants for 7 consecutive day intervals beginning 6 days prior to Day 1 and 7 day intervals around each visit from Weeks 5 to 25. The 7th day of collection for each visit should occur during the Visit Window for Weeks 5 to Week 25.
[9] On clinic visit days, PROs are to be the first assessments performed.
[11] Dosing is daily from Day 1 to Week 25 including all visit and non-visit days.
[12] Collect unused study medication, perform drug accountability (pill count) and document compliance with protocol instructions.

Period	Screening	Treatment															EOS
Visit Name	Screening 2	Treatment										EOT					EOS[20]
Visit Numbers[1]	1	100					110	120	130	140	150	160					1999
Days	-56 to -1	1					29 +5	57 +5	85 +5	113 +5	141 +5	169 +5					199 ±5
Weeks	-8 to -1	1					5	9	13	17	21	25					29
Time (post-dose)	-	Predose	0min	15min	45min	120min	-	-	-	-	-	-	0min	15min	45min	120min	-

[13] As per local requirements (such as United Kingdom investigational sites), Day 1 Predose pregnancy tests can be serum and conducted with the investigator's local lab in order to ensure results are available prior to first dosing. In UK investigational sites, a negative serum pregnancy test must be available no more than 7 days prior to first dosing. Where this is not required, a negative urine pregnancy test must be available prior to dosing on Day 1.
[14] Must occur 15 or more business days prior to planned randomization.
[15] +/-5 min
[16] +/- 15 min
[17] + 1 h
[19] To be completed within 20 days of randomization (and may occur up to pre-dose on Day 1)
[20] EOS visit may be skipped if participant joins the extension study associated with this protocol.
[21] CCI [redacted]

8.1 Screening

It is permissible to re-screen a participant if s/he fails the initial screening, if deemed feasible or necessary by the study site investigator. Participants who do not meet inclusion due to out of range PVR should not be re-screened. If a subsequent re-screen is required after the first permissible re-screening, the case should be discussed with the Sponsor. Additional re-screenings may be approved on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to first dose of study treatment. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Eligibility screening

8.1.1.1 Lung Function Testing

If historical lung function test results are not available within 24 months of screening, then lung function testing, as per investigator's local procedures, must be conducted during screening to confirm eligibility.

The following parameters must be reviewed by the PI:

- Total Lung Capacity (TLC)
- Forced Vital Capacity (FVC)
- Forced Expiratory Volume during the first second (FEV1)

TLC can be done by either body or dilution methods.

FEV1 and FVC must be measured after bronchodilator is administered. Note, the bronchodilator must be locally procured by the Investigator.

Results for the TLC, FEV1, and FVC at screening or historical results must be captured on the appropriate Case Report Form.

8.1.1.2 Hepatitis screen, HIV screen

Not applicable.

8.1.1.3 Alcohol test, Drug screen, Urine cotinine

Not applicable.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for SAE reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. Smoking history will be recorded, as well.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

Pharmacodynamic samples will be collected at the time-points defined in the Assessment Schedule (Table 8-1). Pharmacodynamic samples includes the following assessments:

- NT-proBNP
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

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 8-1).

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 [redacted]

The methods for assessment and recording are specified in the imaging charter and imaging manual. 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 wellbeing of the participant.

8.3.2 Right Heart Catheterization (RHC)

The RHC assessment is performed to assess several hemodynamic variables in pulmonary hypertension, including mPAP, PCWP, CO, PVR, and systemic vascular resistance (SVR).

- 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 patient's concomitant medication and study treatment relative to catheterization should be the same for the subsequent catheterization.
- The following hemodynamic parameters will be assessed when the patient is in a stable hemodynamic rest state (as demonstrated by three consecutive CO measurements within 10% of each other) while the patient 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 for the baseline and Week 25 RHC measurements.

- The following parameters will be derived from the CO measurement:

- SVR in dyn·s/cm^5
- PVR in dyn·s/cm^5

A more detailed instruction manual on the course of the assessments will be provided separately.

8.3.3 Six Minute Walk Test (6MWT)

A standardized 6MWT will be performed considering the guidance for the test procedures described by ERS and ATS guidelines (Holland et al 2014). 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 patient 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 patient 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.

Before randomization, the 6MWT must be performed (between screening and pre-dose on Day 1). The qualifying 6MWT must meet Inclusion Criterion #8 and be within 20 days of randomization.

Single 6MWTs will be performed according to the Assessment Schedule (Table 8-1). 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

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 10.1.1).

As per Section 4.6, 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 4 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.

Clinically notable safety findings are defined in Appendix 1, Section 16.1.

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. A short physical exam will include the examination of general appearance, heart, lungs, abdomen, and extremities (edema). A short physical exam can occur starting from Week 5 except where a complete physical examination is required (see above). 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 eCRF 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, oral or forehead 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.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

8.4.1 Laboratory evaluations

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.

If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

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.

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

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 mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Clinically notable laboratory findings are defined in Section 16.1.

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Erythrocyte, Mean Corpuscular Hemoglobin, Erythrocyte Mean Corpuscular HGB Concentration, Erythrocyte Mean Corpuscular Volume, Platelets, Erythrocytes (will only be assessed in case of abnormalities in the full blood count), Leukocytes, Erythrocyte Cell Morphology differential, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry (Note: thyroid and endocrine function tests are to be conducted at all time points where clinical chemistry is indicated)	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

Test Category	**Test Name**
	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	
Pregnancy Test	Serum pregnancy test refer to 'Pregnancy and assessments of fertility' section
Coagulation Assays	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). These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 16.2 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 16.3. 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, leukocyte esterase, blood, nitrites, pH, protein, specific gravity, urobilinogen)), urine sediment and microscopy
Additional tests	NT-proBNP (considered a pharmacodynamic biomarker)

8.4.2 Electrocardiogram (ECG)

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

Single local 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 eCRF. 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 eCRF. 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.

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

8.4.3 Pregnancy and assessments of fertility

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 up to 24 hours after last study drug administration. In addition, male participants should not donate sperm for the duration of study treatment up to 24 hours after last study drug administration.

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

If participants cannot visit the site to have serum pregnancy tests 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, 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

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy

2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, CCI testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Appropriateness of safety measurements

CCI

Cardiac function and status is 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 (PROs)

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 patient 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.

On visit days and when required, 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. Handling of protocol deviations can be modified if needed per study protocol.

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

If self-administered:

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 stored electronically in the database will be considered the source file.

Completed measures (including when using paper PRO measures and any unsolicited comments written by the participant) 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, study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10.1.1 of the study protocol.

8.5.2 Pharmacokinetics (PK)

Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information (See Section 8.5.3.2)

PK samples will be evaluated in all participants providing samples except the placebo group.

Samples taken for pharmacokinetic analysis will be processed to plasma and concentrations of LTP001 will be quantified by LC-MS-MS. Samples will be collected on Day 1 and Week 25, as per the assessment schedule (Table 8-1).

A non-validated method may be used for metabolite investigations/ exploratory work.

Concentrations will be expressed in mass per volume units and will refer to the free base.

Concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard pharmacokinetic abbreviations and definitions, see the list provided in Section 12.5.1.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental analysis with Phoenix WinNonlin (Version 8 or higher): Cmax and Tmax, from the plasma concentration-time data.

8.5.3 CCI

CCI

CCI

CCI

[redacted]

8.5.3.1 CCI

CCI

8.5.3.2 CCI

CCI

8.5.4 CCI

CCI

CCI

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 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
- Any situation in which continued study participation might result in a safety risk to the participant
- Deterioration of PAH requiring hospitalization
- Development of heart failure symptoms consistent with pulmonary hypertension WHO Functional Class IV (symptoms at rest; severe symptoms at exercise)
- Lung transplantation required
- Atrial septostomy required
- Additional PAH directed therapy required beyond the scope of allowed concomitant medication Section 6.2.1) due to disease progression
- Adverse event that is graded severe by the investigator and considered study drug related
- If a liver or renal event occurs, follow guidelines outlined in Section 16.2 *(*Appendix 2) and Section 16.3 (Appendix 3) regarding discontinuation of study treatment.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

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 Section 8).

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

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

9.1.2 Discontinuation from 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 the Assessment Schedule (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, 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.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

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 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/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

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

9.3 Study stopping rules

Overall study stopping rules

- Three or more (in different participants) similar study-treatment (LTP001) related SAEs; (Exception: SAEs that are related to worsening of PAH (i.e. lack of efficacy by LTP001)).
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold. The sponsor may trigger a safety review in such instances at any time during the study.

In these cases, ad hoc internal experts in collaboration with the DMC and with representative site investigators (if deemed necessary) will carefully evaluate the safety data of the entire study. If time permits – after consultation of the DMC – the sponsor may ask the DMC to undertake a separate review and provide recommendations to the sponsor. The experts (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 findings and recommendations will be documented and will be made available to all investigators, their respective Institutional Review Board/Independent Ethics Committee (IRB/IEC), as appropriate.

Any subjects 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 in consultation with the DMC. 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.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that of the last participant visit following the decision.

For participants that are enrolled in an extension study the corresponding rules of the extension study protocol apply. If the last participant enrolls in the extension study protocol, then the final visit in this protocol for that participant will be considered their Study Completion visit.

9.5 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 based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

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 sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 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 10.1.2):

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 10.1.2 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 permanent (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 participant with the underlying disease.

10.1.2 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
- 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.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

10.1.3 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, under no circumstances later than within 24 hours of learning of its occurrence. 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, and under no circumstances later than 24 hours of the investigator receiving the follow-up information. 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.

10.1.4 Pregnancy reporting

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.

10.1.5 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.

Medication errors are usually unintentional, although a participant can intentionally 'commit' a medication error due to a lack of medical knowledge or sound judgment CCI [redacted]) or there is an accidental drug omission by an HCP). This section can be edited as per trial need.

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 eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. 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.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 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 16-1 in Appendix 2 for complete definitions of liver laboratory triggers /liver events.

Once a participant is exposed to study treatment, every liver event defined in Section 16.1 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) should be repeated to

confirm the 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 eCRF.
- If the initial elevation is confirmed and a liver event is suspected, 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, Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- 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.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase > 25% compared to baseline
- Any one of the following:
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings should be confirmed within 5 days.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff. Please see Table 16-4 for further guidance.

10.3 Committees

10.3.1 Data monitoring committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. Note: the trial statistician will be employed as a member of the 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 a trial.

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

The DMC will also advise the Sponsor in case an unplanned safety review is triggered and requires a decision to stop or continue the study (as per Section 9.3).

11 Data Collection and Database management

11.1 Data collection

All other data captured for this study will have an external originating source (either written or electronic) with the eCRF 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 Case Report Forms (eCRF). 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 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 (recorded on eCRFs) (entered into 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.

11.1.1 Data collection for offsite procedures

The OHPs will enter data at off-site visits into electronic source documentation forms contained in an eSource 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.

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.

11.2 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.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and 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.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant

records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. 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/ delegated CRO/ CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. 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 give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

12.1 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 who received any study drug.

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact PK data.

The PD analysis set will include all participants with available PD data and no protocol deviations with relevant impact on PD data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group and overall utilizing the safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by treatment group.

12.3 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) by treatment group and overall will be summarized 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, by treatment group.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is PVR, defined as the resistance against blood flow from the pulmonary artery to the left atrium measured in dyn·s·cm−5.

12.4.2 Statistical model, hypothesis, and method of analysis

Primary endpoint – Pulmonary Vascular Resistance (PVR)

The change from baseline in PVR at Week 25 will be analyzed using a Bayesian approach (Fisch et al 2015) with Analysis of Covariance. The model includes treatment and WHO functional class as fixed effects and baseline value as a covariate. Contrast for treatment difference will be provided together with 80% two-sided credible intervals under Bayesian framework and the posterior probability that the treatment effect better than placebo will be derived.

To derive the prior distribution for the change from baseline in the placebo group, a meta-analysis (Neuenschwander et al 2010) on the change from baseline in PVR at Week 17/24 for the placebo groups (64 participants) from two historical clinical trials was conducted (Table 12-1). From this meta-analysis, the prior distribution for the change from baseline in PVR in the placebo group is a normal distribution with mean 38.5 $dyn \cdot s \cdot cm^{-5}$ and standard deviation 86.7 $dyn \cdot s \cdot cm^{-5}$, which corresponds to approximately 8 participants for the placebo group. This prior was used as a weakly informative prior for the placebo group at Week 25.

Table 12-1 Historical data used for the meta-analysis to determine the informative prior on PVR for the placebo group

Trial	N	Treatment	Change from baseline (SE)
Selexipag PII	42 (3:1)	Selexipag (n=32)	-129.8 (54.8)
Sotatercept PII (PULSAR)	106 (~2:1)	Placebo (n=32)*	-16 (35.3)

* Placebo arm represents patients on Standard of Care which may include Selexipag.

12.4.3 Handling of intercurrent events of primary estimand

Not applicable.

12.4.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

12.4.5 Sensitivity analyses

The primary analysis will be repeated assuming a non-informative prior for placebo treatment group. This would allow us to capture the results without using any historical control data.

In the event of protocol deviations relevant for inclusion criteria or documented as any deviations from the standardized procedures for PVR collection, the primary analysis will be repeated excluding these subjects.

The underlying normality assumption for analysis of covariance (ANCOVA) will be evaluated. If normality assumption is not met, then alternative methods will be considered such as Hodges-Lehmann, or log-transformed data.

12.4.6 Supplementary analysis

Not applicable.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Change from baseline for 6MWT will be analyzed based on mixed model repeated measures, adjusting for effects of treatment, visit as categorical factors and treatment*visit and baseline*visit interactions. Model based estimates of the mean effect will be reported for each treatment group along with the treatment difference, the 2-sided 80% confidence interval for treatment difference, and one-sided p-value.

Other efficacy endpoints including RHC, echocardiography parameters, PROs (emPHasis-10 and PAH-SYMPACT scores) and NT-proBNP will be summarized as change from baseline by visit and treatment group. Time to clinical worsening will be analyzed using survival models (i.e., Kaplan-Meier, cox regression) if adequate number of events occur during the study to characterize the survival curve. The hazard ratio and the corresponding 80% confidence intervals will be computed using the appropriate method.

If normality assumption is violated for any of the continuous outcomes, then appropriate transformation (i.e., log-transformed) of the data will be considered.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings will be presented by treatment group and tables will be presented by treatment group and overall.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to the EOS visit (about 30 days after the date of the last actual administration of any study treatment).

Adverse events

All adverse events summarized will be displayed by treatment group and overall. All adverse events listing will be presented by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation. In case of sparse events in any of these categories occur, only a listing will be provided if deemed adequate.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics and graphical presentations (e.g. boxplots) will be provided by treatment and visit/time.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted (locally).

Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced (by treatment group).

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics and graphical presentations (e.g. boxplots) will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by by visit/time for treatment group, and overall. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

Descriptive summary statistics of LTP001 plasma concentration data will be provided by treatment, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum.

Descriptive summary statistics for LTP001 PK will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Table 12-2 Non-compartmental pharmacokinetic parameters

Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng x mL-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)

12.5.4 PK/PD relationships

No preplanned analyses is considered. CCI [redacted].

12.6 Analysis of exploratory endpoints

12.6.1 CCI [redacted]

CCI [redacted]

12.6.2 CCI [redacted]

CCI [redacted]

12.7 Interim analyses

An unblinded interim analysis (IA) will be planned for this trial.

The IA will be performed primarily to assess futility (non-binding) on PVR endpoint when approximately 20 participants complete the treatment period (Week 25). In addition, this IA will be utilized to evaluate safety, and efficacy relevant to other endpoints.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Pulmonary Vascular Resistance (PVR)

Approximately 44 participants including dropouts are planned to be randomized in a 3:1 ratio to receive LTP001 vs. placebo on top of Standard of Care (SoC). Dropout rate is considered to be around 10%.

The sample size calculation was based on the primary endpoint of change from baseline in PVR at Week 25. The criteria for this calculation is based on dual criteria:

1. An average change from baseline for PVR over placebo is 100 $dyn \cdot s \cdot cm^{-5}$ and

2. 90% level of proof that the change from baseline for PVR in the LTP001 group is better than placebo.

With a non-informative prior for the LTP001 group, and the obtained weakly informative prior for the placebo group, a sample size of 40 (3:1 ratio of LTP001: placebo) provides approximately 86% chance (power) of meeting the success criterion. Refer to Section 12.4.2 for further details. With approximately 20 participants completing the study at interim, the probability of considering stopping early for futility (non-binding) is approximately 47% in case of a placebo-like drug and approximately 1% in case the true treatment difference for PVR is 200 $dyn \cdot s \cdot cm^{-5}$, which is the statistically significant difference between drug and placebo in this PAH population.

Assumptions related to PVR variability will be evaluated at the time of interim analyses to consider re-estimation of sample size as appropriate.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign 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. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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 patient 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.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 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

14 Protocol adherence

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.

14.1 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.

15 References

References are available upon request.

Beshay S, Sahay S, Humbert M (2020) Evaluation and management of pulmonary arterial hypertension. Respir Med p. 106099.

Fisch R, Jones I, Jones J, et al (2015) Bayesian Design of Proof-of-Concept Trials. Ther Innov Regul Sci p. 155-162.

Hemnes AR, Humbert M (2017) Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. Eur Respir Rev.

Holland AE, Spruit MA, Troosters T, et al (2014) An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J p. 1428-46.

CCI [redacted]

Murakami K, Mathew R, Huang J, et al (2010) Smurf1 ubiquitin ligase causes downregulation of BMP receptors and is induced in monocrotaline and hypoxia models of pulmonary arterial hypertension. Exp Biol Med (Maywood) p. 805-13.

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials p. 5-18.

Rothman AM, Arnold ND, Pickworth JA, et al (2016) MicroRNA-140-5p and SMURF1 regulate pulmonary arterial hypertension. J Clin Invest p. 2495-508.

CCI [redacted]

Wilkins MR, Aman J, Harbaum L, et al (2018) Recent advances in pulmonary arterial hypertension. F1000Res.

CCI [redacted]

Zhu H, Kavsak P, Abdollah S, et al (1999) A SMAD ubiquitin ligase targets the BMP pathway and affects embryonic pattern formation. Nature p. 687-93.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

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

QRS-Duration > 120 ms when normal at baseline.

PR - value > 220 ms when normal at baseline

AV-block > Grade 2a

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?)

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

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 16-1 in Appendix 5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 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.

1. 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.
2. If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
3. Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1 Discontinuation from study treatment), if appropriate
4. Hospitalization of the participant if appropriate
5. Causality assessment of the liver event
6. 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.

Table 16-1 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 16-2 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	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.
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 5 x ULN 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.
	If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for			

	ALT	TBL	Liver Symptoms	Action
	more than two weeks			• 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	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (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)

Criteria	**Actions required**	**Follow-up monitoring**
> 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

16.3 Appendix 3: 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. Further guidance for the follow-up of abnormal renal function parameters and renal events will be provided in the investigator portal under Renal Events guidance document.

Table 16-4 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase > 25% fold compared to baseline	Follow up within 1-2 days Please review Section 8.4.1
Urine Event	
New onset dipstick proteinuria ≥3+ OR	Follow up within 2-5 days
New onset dipstick hematuria ≥3+ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)	Please review Section 8.4.1
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).	

16.4 Appendix 4: Calculation of Pulmonary Vascular Resistance (PVR)

$$\text{PVR} = \frac{mPAP\ (mmHg) - PCWP(mmHg)}{CO\ (\frac{L}{\text{min}})}\ x\ 80$$

PVR = Pulmonary Vascular Resistance
mPAP = Mean Pulmonary Arterial Pressure
PCWP = Pulmonary Capillary Wedge Pressure
CO = Cardiac Output