NOVARTIS

Clinical Development

LTP001

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

Statistical Analysis Plan (SAP)

Document type:	SAP Amendment 2
Document status:	Final
Release date:	05-Jun-2024
Number of pages:	25

Document History – Changes compared to previous final version of SAP


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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of covariance
BMI	Body Mass Index
CO	Cardiac Output
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in the first second
HR	Heart Rate
IA	Interim Analyses
LLOQ	Lower Limit of Quantification
MAR	Missing at random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligram(s)
mL	Milliliter(s)
mPAP	Mean Pulmonary Arterial Pressure
NT-proBNP	N-terminal fragment of the prohormone B-type Natriuetic Peptide
OHP	Off-site Healthcare Professional
PD	Pharmacodynamic(s)
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PVR	Pulmonary Vascular Resistance
QTcF	QT interval corrected by Fridericia's formula
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SoC	Standard of Care
TAPSE	Tricuspid Annular Plane Systolic Excursion
TASV	Tricuspid Annular Systolic Velocity
TFLs	Tables, Figures, Listings
TTCW	Time to Clinical Worsening
WHO	World Health Organization
PAH	Pulmonary Arterial Hypertension
SAP	Statistical Analysis Plan
6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test

1 Introduction

The Reporting and Analysis documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CLTP001A12201".

This Statistical Analysis Plan (SAP) has been developed in accordance with Clinical Trial Protocol CLTP001A12201 (Amended Protocol Version 02, released on 01-Mar-2022), and describes the implementation of the statistical analysis planned in the protocol.

1.1 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.

The study design is described in Figure 1-1. A screening period of 8 weeks will be used to access eligibility prior to randomization. Approximately 44 eligible participants with PAH will be randomized in a 3:1 ratio to either oral LTP001 or placebo daily for 24 weeks in order to achieve 40 patients who complete the treatment period.

An unblinded interim analysis 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.

Figure 1-1 Study design scheme

Participants may be allowed to roll over from this study to enter the open label extension study upon approval from health authorities and review boards.

1.2 Study objectives, endpoints and estimands

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

Objective(s)	Endpoint(s)
• 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
	  • 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	

1.2.1 Primary estimand(s)

Not applicable.

2 Statistical methods

2.1 Data analysis general information

2.1.1 General definitions

Investigational treatment will be LTP001 or placebo.

Date of first administration of study treatment (Day 1) will be defined as the date of the first actual administration of LTP001 or placebo.

Date of last administration of study treatment will be defined as the date of the last actual administration of LTP001 or placebo.

Baseline will be defined as the Day 1 assessment. If this datum is not available, the last pre-dosing assessment will be considered.

Study day will be defined as the number of days since the date of first dose of study treatment (LTP001 or placebo). The date of first dose of study treatment will be defined as Day 1 and the day prior to first dose of will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

for dates on or after the date of first dose of study treatment,

Study day = Assessment date – Date of first dose administration + 1

The on-treatment period lasts from the date of first administration of study treatment to the End of Study (EOS) visit or the date of last randomized dose if EOS visit is not available. The EOS visit is a follow-up visit that is approximately 30 days after the date of the last actual administration of investigational treatment. For participants who will be enrolled into the open label extension (OLE) study, their EOS visits will be skipped.

2.2 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. Participants in the placebo arm will be excluded from PK analysis set.

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

The analysis sets and protocol deviation codes are related as Table 2-1.

Table 2-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from Safety analysis in case of these PDs:		**Exclude subject from Safety analysis set**
WITH01	Subject withdrew consent but continue to receive study medication	Y
Subjects are excluded from PK analysis in case of these PDs:		**Exclude subject from PK analysis set**
WITH01	Subject withdrew consent but continue to receive study medication	Y
CCI	CCI	Y
Subjects are excluded from PD analysis in case of these PDs:		**Exclude subject from PD analysis sets**
WITH01	Subject withdrew consent but continue to receive study medication	Y
INCL04	Absence of history of PAH subgroups of clinical classification group 1 as defined in Protocol	Y
INCL05A	Resting mPAP is <25 mmHg, PCWP or left ventricular end diastolic pressure >15 mmHg as determined by RHC	Y
INCL06A		Pulmonary Vascular Resistance is <6 WU corresponding to 480 dynes s/cm5 as determined by RHC
INCL07	Patient doesn't have PAH of WHO Functional Class II – III	Y
EXCL03	Patients with PH in clinical classification groups 2-5 (WHO) and any PAH group 1 subgroups not covered by IE 4	Y
CCI	CCI	Y

Protocol deviations mentioned above, and analysis sets will be reviewed in the data review meeting to decide inclusion or exclusion of participant(s) from analyses sets. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to final database lock (DBL).

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

A summary table will be presented including the number and percentage of participants

- Who were randomized to treatment groups and overall
- Who completed the study
- Who discontinued from study (overall and by the primary reason for discontinuation)

The number and percentage of participants in each analysis set will be tabulated by treatment group. The percentage will be based on all randomized participants.

A listing of all participants excluded from any analysis sets will be provided with reasons for exclusion (i.e., including both protocol and non-protocol deviations)

2.3.2 Demographics and other baseline characteristics

Demographics 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.

Participant demographics will include age, gender, race, ethnicity & BMI.

The following clinical baseline characteristics will be summarized separately:

- Time since PAH diagnosis
- PAH classification
- Standard of care
- Smoking history
- WHO functional Class
- 6 Minute Walk Test and Borg Scale
- PVR
- Echocardiography parameters
- Lung function test
- NT-proBNP
- Concomitant PAH medication (classified as per the inclusion criteria; prostacyclin analogues and receptor agonists
- endothelin receptor antagonists
- phosphodiesterase type 5 inhibitors

- soluble guanylate cyclase stimulators)

Relevant medical history and current medical conditions at the baseline will be listed by the treatment group and participant.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The Safety set will be used for treatment related summaries. Categorical data will be summarized as frequencies and percentages. For continuous data, N, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

2.4.1 Study treatment / compliance

On Day 1, all eligible participants will be randomized and assigned in a 3:1 ratio to receive either LTP001 or placebo. The study medication (LTP001 [redacted] mg or placebo) will be taken daily at approximately the same time each day [redacted]. LTP001 [redacted] mg consists of [redacted]

The treatment period is for 24 weeks with participants' visits at week 1, week 5, week 9, week 13, week 17, week 21, week 25. Participants are instructed to take the study treatment exactly as prescribed and 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. The information will be captured in the source document at each visit. All study treatment dispensed and returned will 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.

Participants will 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.

Pill counts (including counts of dispensed/returned pills) will be listed by participants, and visits, with relevant information about compliance provided by the participant if data is available.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment for participants in the safety set will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

To assess the efficacy of LTP001 in participants with pulmonary arterial hypertension (PAH), the primary endpoint of the study will be the change from baseline in Pulmonary Vascular Resistance (PVR) at Week 25. PVR is defined as the resistance against blood flow from the pulmonary artery to the left atrium measured in dyn·s·cm−5.

2.5.2 Statistical hypothesis, model, and method of analysis

The analysis will be performed on the PD analysis set. The change from baseline in PVR at Week 25 will be analyzed using a Bayesian approach (Fisch, et al., 2015) 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, Capkun-Niggli, Branson, & Spiegelhalter, 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 2-2). 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·s·cm−5 and standard deviation 86.7 dyn·s·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 2-2 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 SoC which may include Selexipag.			

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

2.5.5 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.

Due to the fact that the WHO functional classification tents to be sparse, a model without WHO functional classification will be fitted.

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.

An analysis of covariance (ANCOVA) will be conducted with treatment as fixed effect and baseline as covariate to support the result of the primary analysis.

An analysis of residuals will be carried-out to assess model assumption. If the underlying normality assumption for analysis of covariance (ANCOVA) is not met, then alternative methods will be considered such as Hodges–Lehmann (Lehmann & Hodges, 1963) or log-transformed data.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

All analysis of secondary endpoints will be performed on the PD analysis set. Missing data for any reason will not be explicitly imputed and will be handled by the respective mixed effects model (if performed) which implicitly imputes missing data assuming missing at random (MAR).

2.6.1 Secondary endpoint(s)

Six Minute Walk Test

This measures how many meters a person can walk in 6 minutes. It includes total distance walked (6MWD), the number and duration of any stops in 6 minutes. Test performed at baseline and at visits on Week 13, and 25 will be used for analysis.

Right Heart Catheterization (RHC)

The RHC is performed to assess several hemodynamic parameters when the patient is in a stable hemodynamic rest state (as demonstrated by three consecutive cardiac output measurements with 10% of each other). The measurement is taken at baseline and at visit on Week 25. The assessed hemodynamic parameters include:

- right atrial (RA) pressure
- mean pulmonary artery pressure (mPAP)
- pulmonary capillary wedge pressure (PCWP)
- systolic and diastolic blood pressure (RV pressures)

- heart rate (HR)
- cardiac output (CO)
- systemic vascular resistance (SVR)
- mixed venous blood gas measurement

Echocardiography

The echocardiography is performed to assess the impact of study drug on right heart structure and function. All echocardiography images will be centrally read by an imaging vendor. The measurement is taken at baseline and at visit on Week 5, 13, and 25.

The assessed echocardiography parameters include:

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

Patient Reported Outcomes (PROs)

The two patient reported outcomes utilized in this study are emPHasis-10 and in PAH-SYMPACT. Change from baseline on Week 13, and 25 will be descriptively summarized.

- The emPHasis-10 questionnaire (Yorke, et al., 2014) consists of 10 items that address breathlessness, fatigue, control and confidence. Each item is scored on a semantic differential six-point scale (0-5) and carries the same weight. Hence, a total emPHasis-10 score is derived simply aggregating scores of the 10 items. It ranges from 0 to 50, with higher scores representing a higher symptom burden.
- The PAH-SYMPACT questionnaire (Mccollister, et al., 2016) (Chin, et al., 2018) consists of 11 symptom items across two domains (cardiopulmonary and cardiovascular symptoms) and 11 impact items across two domains (physical and cognitive/emotional impacts). Symptom items and one item about the use of oxygen are assessed daily for one week; impact items are assessed on the last day of the week. Each item is scored on a five-point scale (0-4) except for the item of using oxygen (scale 0-1). The total PAH-SYMPACT score will be calculated as the sum of impact item scores and mean weekly symptom item scores. For each symptom item, its mean weekly score will be calculated as the average daily item score taken within the 7-day interval.

NT-proBNP

The N-terminal fragment of the prohormone B-type natriuetic peptide (NT-ProBNP) is reflective of right ventricular distress. Measurements collected at baseline and at visits on Week 13, and 25 will be used for analysis.

Time to clinical worsening (TTCW)

TTCW will be defined as time to any of the following events:

- Death

- Hospital stay (≥ 24 h) due to worsening of PAH.
- 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
- Significant drop in 6MWD (15% from baseline or more) due to PAH-worsening

2.6.2 Statistical hypothesis, model, and method of analysis

6MWT

Change from baseline in walked distance for 6MWT at visits 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

TTCW

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. Participants without the event will be considered as censored at the end of the time at risk. The hazard ratio and the corresponding 80% confidence intervals will be computed using the appropriate method. If there is no adequate number of events, the number (and percentage) of participants with clinical worsening will be summarized by treatment and overall.

Echocardiography

Descriptive statistics (N, mean, SD, CV% mean, geometric mean, CV% geometric mean, median, min, and max) summarizing echocardiography parameters and their changes from baseline will be summarized by visit for treatment group and overall.

Panels of individual spaghetti plots over time/visit for each echocardiography parameter will be provided.

All echocardiography parameters will be listed by participant, and visit and if ranges are available, abnormalities will be flagged.

PROs

For emPHasis-10, total score and change from baseline of total score will be summarized by visit for treatment and overall. For PAH-SYMPACT, the total score and change from baseline will be summarized by visit for treatment and overall.

NT-proBNP

NT-proBNP (visits on week 13 and 25) will be analyzed based on mixed model repeated measures, adjusting for the baseline, treatment groups, visit and treatment-by-visit interaction. 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. Depending on the distribution of NT-proBNP data, the analysis for NT-proBNP might be through logarithms to reduce outliers and skewness.

RHC

RHC parameters and their change from baseline will be summarized by visit for treatment group and overall.

Echocardiography parameters, PROs, and RHC are all continuous variables. Summary statistics (including N, mean, SD, minimum, median, and maximum) of each parameter, and graphical presentations (e.g., boxplots) will be provided by visit/time for treatment group, and overall

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent events

Missing data will be assumed MAR while imputing the missing values.

2.6.5 Sensitivity analyses

For the analysis of 6MWT, missing measurement will be assumed MAR. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

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 except for baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

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).

2.7.1 Adverse events (AEs)

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. The definition of the on treatment period is defined in Section 2.1.1.

- 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.

2.7.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.7.2 Deaths

The number and percentage of deaths, including on-treatment and post-treatment deaths, will be summarized by treatment group.

2.7.3 Laboratory data

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Descriptive statistics (N, mean, SD, minimum, median, and maximum) summarizing continuous laboratory results of clinical chemistry, hematology, urinalysis, and changes from baseline by visit/time for treatment group, and overall will be provided. Graphical presentations (e.g., boxplots) will be provided by visit/time and treatment.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value for treatment group.

2.7.4 Other safety data

2.7.4.1 ECG data

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 QTcF (Fridericia's formula) interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT or QTc intervals or changes from baseline will be presented. The number and percentage of participants with clinical notable QTcF will be summarized by visit and treatment group and overall. A listing of these participants will be produced (by treatment group). The clinical notable criteria for QTcF (Fridericia's formula) are indicated in Table 2-3.

Table 2-3 Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTcF (msec)	> 500
QTcF (msec)	> 480 if normal at baseline
Notable change from baseline	
QTcF (msec)	> 60

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.

2.7.4.2 Vital signs

Vital signs will include the collection of otic or oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics (including N, mean, SD, minimum, median, maximum) of vital signs and changes from baseline will be provided by visit/time for treatment group and overall. Graphical presentations (e.g., boxplots) of vital signs will be provided by treatment and visit/time.

2.8 Pharmacokinetic endpoints

All subjects within the PK analysis set will be included in the PK data analysis.

The following pharmacokinetic parameters will be determined using PK blood samples collected at visits on CCI

- LTP001 plasma concentration
- Cmax and Tmax

Cmax (in ng/mL) is the maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration. Tmax (in hour) is the time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration.

Descriptive summary statistics of LTP001 plasma concentration data will be provided by treatment, and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and the frequency (n, %) of concentrations below the LLOQ will be reported. The geometric mean will not be reported if the dataset includes zero values.

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.

2.9 PD and PK/PD analyses

CCI [redacted]

2.10 Patient-reported outcomes

Borg score

For the Borg score component, the participant will answer questions on a scale of one to ten to determine the participant's shortness of breath during the 6MWT. Larger score indicates higher breathing difficulty.

The Borg score and change from baseline will be summarized by visit and treatment group on the PD analysis set.

2.11 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

2.12 Other Exploratory analyses

CCI

[redacted]

CCI

[redacted]

2.13 Interim analysis

An unblinded interim analysis (IA) will be carried-out when approximately 20 participants complete the treatment period (Week 25).

This IA will be performed primarily to assess futility (non-binding) on PVR endpoint. The study may be stopped for futility if the posterior probability of the treatment effect no better than placebo is above 60%. Also, analysis for secondary efficacy endpoints, including right heart catheterization results, PROs, NT-proBNP, 6MWD, and TTCW will be performed as described in Section 2.6.

Safety parameters including clinical safety laboratory, ECG, vital signs, and adverse events will be listed and descriptively summarized by treatment and visit/time, if appropriate. More detailed description of the analyses as described in Section 2.7 will be conducted. The study will be stopped if there are three or more (in different participants) similar study-treatment (LTP001) related SAEs that are not related to worsening of PAH (i.e., lack of efficacy by LTP001)

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. Unblinded interim analysis results will be reviewed by the clinical team.

3 Sample size calculation

Approximately 44 participants including dropouts are planned to be randomized in a 3:1 ratio to receive LTP001 vs. placebo on top of 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 criterion for this calculation is based on dual criteria:

1. An average change from baseline for PVR over placebo is 100dyn·s·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 84% chance (power) of meeting the success criterion if the true treatment effect over placebo is 200 dyn·s·cm^{-5}.

With approximately 20 participants completing the study at interim, the probability of considering stopping early for futility (non-binding) is approximately 44% in case of a placebo-like drug and less than 3% in case the true treatment difference for PVR is 200 dyn·s·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.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Reference

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