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Title:

A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects with Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy

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ABBREVIATIONS AND DEFINITIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood urea nitrogen
CO	Cardiac output
CTD	Connective tissue disease
eCRF	electronic Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
FC	Functional Class
FEV_1	Forced expiratory volume at 1 second
HIV	Human immunodeficiency virus
ITT	Intent-To-Treat
IUD	Intrauterine device
LOCF	Last observation carried forward
LVEDP	Left ventricular end-diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated angiogram
MMRM	Mixed model repeated measurement
NYHA	New York Heart Association
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAPd	Pulmonary artery pressure diastolic
PAPm	Pulmonary artery pressure mean
PAPs	Pulmonary artery pressure systolic
PCWPm	Pulmonary capillary wedge pressure mean
PDE5-I	Phosphodiesterase type 5 inhibitor
PFO	Patent foramen ovale
PT	Preferred term

PVR	Pulmonary vascular resistance
PVRI	Pulmonary Vascular Resistance Index
RBC	Red blood cell
RAPm	Right atrial pressure mean
RHC	Right heart catheterization
SAE	Serious adverse event
SaO_2	Systemic arterial oxygen saturation
SAP	Statistical Analysis Plan
SAPd	Systemic arterial pressure diastolic
SAPm	Systemic arterial pressure mean
SAPs	Systemic arterial pressure systolic
SDF	Survival distribution function
sGC	Soluble guanylate cyclase
SOC	System organ class
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
TID	3 times daily
TLC	Total lung capacity
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

1 PREFACE

This document describes the planned analyses for the TDE-PH-310 clinical study. This plan is based on the original TDE-PH-310 protocol dated 26 Jan 2012 and subsequent protocol amendments (latest version protocol amendment 8 dated 9 Aug 2017), and provides further details of the analyses presented in the protocol as well as additional planned analyses. Additional post-hoc or unplanned analyses that are not defined in this statistical analysis plan (SAP) may be performed. Such analyses will be documented in the Clinical Study Report (CSR).

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is:

To assess the effect of oral UT-15C with pulmonary arterial hypertension (PAH)-approved oral monotherapy compared with placebo with PAH-approved oral monotherapy on time to first clinical worsening event (adjudicated), as defined by at least 1 of the events listed below:

- Death (all causes)
- Hospitalization due to worsening PAH, defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or
  - Lung or heart/lung transplantation; or
  - Atrial septostomy
- Initiation of an inhaled or infused prostacyclin for the treatment of worsening PAH
- Disease progression (all criteria required):
  - A decrease in 6-Minute Walk Distance (6MWD) of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by two 6-Minute Walk Tests (6MWTs) performed on different days.
  - Worsening of PAH symptoms, which must include either:
    - An increase in Functional Class (FC) from Baseline or
    - Appearance or worsening of symptoms of right heart failure since Baseline
- Unsatisfactory long-term clinical response (all criteria required):
  - Randomized to receive study drug for at least 24 weeks

- A decrease from Baseline in 6MWD at Week 24 and beyond at 2 consecutive visits on different days
- Sustained World Health Organization (WHO) FC III or IV symptoms for at least 24 weeks, consecutively

Please note that all time to worsening events reported by the investigators are adjudicated by an independent adjudication committee. The independent adjudication committee is blinded to the treatment assignment.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to assess the effect of oral UT-15C combined with PAH-approved oral monotherapy compared to placebo combined with PAH-approved oral monotherapy on the following:

Key Secondary Endpoints:

- Exercise capacity as assessed by 6MWD measured at Week 24
- Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 24
- Combined 6MWD/Borg dyspnea score at Week 24

Other Secondary Endpoints:

- Exercise capacity as assessed by 6MWD measured at visits other than Week 24
- Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) at visits other than Week 24
- Borg dyspnea score
- WHO FC
- Right heart catheterization (RHC) hemodynamics at Week 24 (optional)

Exploratory Endpoints:

- Optional evaluation of biomarkers
- Optional evaluation of pharmacogenomics

2.3 SAFETY

The safety objective of this study is to assess the safety of oral UT-15C combined with PAH-approved oral monotherapy compared to placebo combined with PAH-approved oral monotherapy on the following:

- Clinical laboratory parameters
- Vital signs
- Adverse events (AEs)
- Electrocardiogram (ECG)

3 STUDY DESIGN

This is an international, multicenter, randomized, double-blind, placebo-controlled, event-driven study in subjects with PAH receiving background oral monotherapy. Subjects will be assessed during the Screening Period to determine eligibility for the study, which will be confirmed during the Baseline Visit prior to randomization. Once randomized, subjects will return for study visits every 4 weeks for the first 12 weeks, then every 12 weeks for the duration of the study. Subjects will continue in the study until they experience clinical worsening, as defined in the protocol, or they prematurely discontinue participation in the study for any reason other than protocol-specific clinical worsening.

If a subject meets the definition of clinical worsening during the study and receives only short-term (28 days or less) treatment with an infused or inhaled prostacyclin therapy for worsening PAH, they will be permitted to enter the open-label extension study (TDE-PH-311). If a subject prematurely discontinues the study for any reason other than clinical worsening, or receives long-term (29 days or more) treatment with an infused or inhaled prostacyclin therapy for worsening PAH, they will not be permitted to enter the open-label extension study.

An interim analysis for efficacy is planned when 75% (154) of the total (205) adjudicated clinical worsening events have occurred. All subjects actively participating in the study will be allowed to transition to the open-label extension study if the interim efficacy analysis is positive. If enrollment continues beyond the interim efficacy analysis, final enrollment will be stopped when approximately 190 clinical worsening (morbidity or mortality) events have been reported by Investigators and reviewed by the Medical Monitor. Subjects will be followed until the occurrence of approximately 205 adjudicated clinical worsening events, at which time all remaining subjects will be transitioned to the open-label extension study. No more than 850 subjects will be enrolled.

At each scheduled visit, subjects will undergo the following efficacy assessments: clinical worsening, exercise capacity (6MWD and Borg dyspnea score), and WHO FC.

Plasma samples will also be collected for measurement of NT-proBNP at Baseline, Week 12, Week 24, Continued Visit 1, and at every other continued visit thereafter.

Additionally, subjects may participate in an optional hemodynamic sub-study in which hemodynamic parameters will be assessed by RHC before randomization at Baseline and following 24 weeks of treatment with study drug.

Safety will be assessed via vital signs, AEs, and clinical laboratory parameters. Subjects will also undergo a 12-lead ECG at Screening and Week 24.

Subjects must receive only 1 PAH-approved oral therapy at a dose that complies with the approved prescribing information for the product for at least 30 days before the day of randomization to participate in the study. The dose of background oral monotherapy may be titrated as clinically indicated during the Screening Period. Subjects must be on a stable dose of their background oral monotherapy for a minimum of 10 days prior to being randomly allocated to receive either oral UT-15C or placebo at randomization. Subjects will receive their first dose of study drug (0.125 mg) in the clinic on the day of randomization. Oral dosing of study drug will be continued at 0.125 mg 3 times daily (TID) every 6 to 8 hours with food. The dose will be slowly titrated up throughout the study to a maximum dose of 12 mg TID in an effort to reach a well-tolerated dose that provides optimal clinical benefit.

4 SEQUENCE OF PLANNED ANALYSES

4.1 INTERIM SAFETY ANALYSES

Interim safety analyses are intended to be performed after approximately 200, 400, and 600 subjects are enrolled in the study, or on an ad hoc basis per request of the independent Data Monitoring Committee (DMC) as necessary. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The sponsor will only have access to blinded study data during this process.

4.2 INTERIM EFFICACY ANALYSIS

One interim analysis for efficacy is planned when 75% (154 events) of the total (205) adjudicated clinical worsening events have occurred. All analyses will be prepared by an independent external consultant and reviewed only by the independent DMC as defined in the DMC charter. The sponsor will only have access to blinded study data during this process. The details of the interim efficacy analysis will be included in a separate SAP for interim analyses.

4.3 FINAL ANALYSIS AFTER DATABASE LOCK AND STUDY UNBLINDING

After the database has been quality assured and locked, the treatment assignments will be provided to the sponsor's project statistician by the central randomization service, and all planned analyses described in this document will be performed. By intent, no changes will be made to these data after unblinding. However, any changes that are deemed absolutely necessary subsequent to unblinding will be clearly documented in the CSR.

5 SAMPLE SIZE CONSIDERATIONS

Approximately 205 adjudicated clinical worsening events will provide at least 90% power with a type I error rate of 0.05 (2-sided hypothesis) to detect a difference in the time to clinical worsening between treatment groups, assuming exponential distributions and an underlying hazard ratio of 0.62. Assuming a placebo median event time of 32 months (which corresponds to an event rate of 23% at Month 12), this hazard ratio corresponds to a median time to event of 51 months for the UT-15C group (which corresponds to an event rate of 15% at Month 12). Further assuming subject accrual is completed during the first 3 years with a 10% dropout rate at the end of the study, a total sample size of at least 610 subjects with a maximum of 850 subjects is expected to generate approximately 205 adjudicated clinical worsening events over the course of the study.

The primary efficacy endpoint of time to adjudicated clinical worsening events will be tested at an interim analysis when 75% of total adjudicated clinical worsening events have occurred with an alpha level of 0.020, and at the final analysis at an alpha of 0.044 with the overall Type I error rate at 0.05. Efficacy boundaries for early stopping of the study for efficacy are calculated based on O'Brien-Fleming alpha-spending function.

6 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) Population is defined as all subjects randomized into the study who received at least 1 dose of study drug. All subjects will be counted as being in the group to which they were randomized, regardless of the treatment they actually received. All original stratification information used in the randomization procedure will be used for analyses, regardless of whether it was later found to be incorrect. All efficacy analyses will be performed primarily on the ITT Population.

The Safety Population is defined as all subjects in the study actually receiving study drug (regardless of randomization), and all subjects will be counted as being in the group corresponding to the treatment that they actually received. If a subject incorrectly received active drug during the study, they will be counted in the active treatment group. All safety analyses will be performed on the Safety Population.

The Per-protocol Population will include all subjects in the ITT Population, excluding subjects with major protocol deviations that may have an impact on the primary efficacy analyses. The major protocol deviations and the subject's exclusion from the Per-protocol Population will be reviewed at a blinded data review meeting and documented prior to the database lock and the study unblinding. The major protocol deviations that exclude the subjects from the Per-protocol Population include, but are not limited to the following:

- Subject had violation of inclusion criterion #5 or exclusion criteria #6
- Subject had violation of exclusion criterion #3
- Subject interrupted intake of study drug for a total of at least 50% of the time between first and last study drug dosing
- Subject had been off-treatment for at least 4 weeks at any point between first and last dosing of study drug in study
- Subject started and continued treatment with any prohibited medications for extensive duration during the study
- Individual unblinding of study drug to the investigator prior to the subject completing the study

7 INTERIM ANALYSES

An independent DMC will be established for the study, composed of 3 members, including 2 physicians knowledgeable in the treatment of PAH and a statistician. Throughout the course of the study, the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur after approximately 200, 400, and 600 subjects are enrolled in the study, or on an ad hoc basis per request of the independent DMC, as necessary. The DMC will be semi-blinded (ie, labelled as Group X and Group Y) to individual subject treatment allocation during the review process, and can be unblinded to individual subject treatment allocation if requested.

In addition, the independent DMC will review the results of a single efficacy interim analysis after 75% of total adjudicated clinical worsening events have occurred (which corresponds to 154 events). For interim efficacy analysis, treatment groups will be unblinded to DMC members.

All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The sponsor will only have access to blinded study data during this process.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All the data collected in the electronic Case Report Form (eCRF) will be listed. In general, listings will be sorted by treatment group, subject number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), study day, and all relevant data collected in the eCRFs. For data collected on a fixed schedule, the assessment identifier will also be included on the listing. Repeat or redundant observations within an assessment window and observations that do not fall within any predefined assessment window (and will, therefore, be excluded from summaries) will be flagged in these listings. Subjects who will not be included in the analysis population (eg, Safety Population, Per-protocol Population) will be flagged.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group. For continuous variables, summary statistics will include the mean, standard

deviation, median, minimum, and maximum. For summaries of non-normal data, such as 6MWD, interquartile range (lower quartile, upper quartile) may also be included. Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal place than was collected. For discrete variables, summaries will include the frequency and percentage in each category. Percentages will be rounded to 1 decimal place. For all inferential analyses and descriptive comparisons, p-values will be rounded to 4 decimal places. Values less than 0.0001 will be denoted as <0.0001, and values greater than 0.9999 will be denoted as > 0.9999. Wherever practical, categories of discrete variables will be ordered and labelled as they appear in the eCRF.

All analyses are performed using the statistical software SAS® (SAS Institute 2015).

8.1 COVARIATES

Primary efficacy analyses of time to clinical worsening will be adjusted for Baseline 6MWD category (≤350 meters versus >350 meters) and background PAH therapy (as a categorical variable: phosphodiesterase type 5 inhibitor [PDE5-I] or soluble guanylate cyclase [sGC] stimulator only versus endothelin receptor antagonist [ERA] only).

The efficacy analyses of change from Baseline in 6MWD at Week 24 and other time points will be adjusted for Baseline 6MWD (as a continuous variable) and background PAH therapy (as a categorical variable: PDE5-I or sGC stimulator only versus ERA only).

The efficacy analyses of change from Baseline in NT-proBNP at Week 24 and other time points will be adjusted for Baseline NT-proBNP.

8.2 EXAMINATION OF SUBGROUPS

For the primary efficacy endpoint (time to adjudicated clinical worsening event), subgroup analyses will be performed. These subgroups will include:

- Background PAH therapy (PDE5-I or sGC stimulator only versus ERA only)
- Etiology of PAH (idiopathic/heritable, associated with collagen vascular disease, and other etiologies)

- Baseline walk categories (≤350 m versus >350 m)
- Baseline WHO FC (class 1-2 versus class 3-4)
- Age group (<65 years versus ≥65 years)
- Sex (male versus female)
- Maximum dose achieved (<9 mg versus ≥9 mg total daily dose)
- Geographic region, categorized as North America (United States and Canada), Asia-Pacific (China, Taiwan, India, Australia, Singapore, South Korea), Europe (Germany, United Kingdom, Israel, Italy, Netherlands, Poland, France, Denmark, Greece, Austria, and Sweden), and South and Latin America (Mexico, Brazil, Chile, and Argentina)

Similarly, the subgroup analyses for subgroups listed above will also be performed for the key secondary endpoint of change from Baseline in 6MWD at Week 24.

No adjustment for multiplicity will be performed for these subgroup analyses.

8.3 PREMATURE DISCONTINUATION AND MISSING DATA

Clinical worsening events are evaluated up to the end of the study. In this event-driven study, at the end of the study, some subjects will not have clinical worsening events; some will discontinue the study early or be lost-to-follow-up before experiencing a clinical worsening event. For the time to clinical worsening event data, a censoring algorithm will be employed.

The 6MWD and other secondary efficacy endpoints are evaluated up to the end of the study; however, the analyses are mainly focused on the data up to Week 48. For 6MWD and other key secondary efficacy endpoints, missing data will be imputed as described in the sections below.

8.3.1 Missing Data Handling for Time to Clinical Worsening

For the analysis of time to clinical worsening, subjects who do not have an adjudicated clinical worsening event will be censored at the time of their last known study drug dose. For subjects who are reported as having a clinical worsening event by the Investigator and subsequently are classified as not having a clinical worsening event by the adjudication committee, the time to clinical worsening is also censored at the time of their last assessment date. For subjects who dropped out of the study early without experiencing a clinical

worsening event, the subjects will be censored at the time of their last assessment prior to down-titration or discontinuation of study drug.

In addition, the following 2 additional analyses will be performed on the primary efficacy endpoint (adjudicated time to clinical worsening) to assess the impact of missing data:

1. Early termination treated as clinical worsening event
2. Early termination due to AEs treated as clinical worsening events

For the mortality analysis, the vital status (live/dead status) for all subjects will be collected throughout the study to the study closure (the last patient last visit). Vital status for subjects who discontinued the study early is included in this mortality analysis. If the vital status is unknown at study closure, the time to death will be censored at the last known date the subject is alive.

8.3.2 Missing Data Handling for 6MWD

For the analysis of 6MWD, subjects may not have completed the treatment with study drug prior to the Week 48 visit for the following reasons: death, clinical worsening (per protocol definition), progressive disease (not meeting protocol definition of clinical worsening), AE unrelated to disease, withdrawal of consent by the subject, protocol deviation, loss to follow-up, termination of study by the sponsor, or withdrawal for other reasons. Every attempt must be made to perform all efficacy assessments immediately prior to premature termination of study drug or within 6 hours of the final study drug dose. In addition, subjects still receiving study drug may be too clinically ill to perform the 6MWT, resulting in missing data for that assessment.

In the analyses of 6MWD using nonparametric and parametric analysis of covariance methods, for subjects whose 6MWD measures at visits up to Week 48 are missing, the missing value will be imputed.

- For those subjects who have no 6MWD measurement due to death, too ill to perform 6MWT, or clinical worsening event, the 6MWD is set to the worst score of 0 meter.
- For missing data at visits prior to death or clinical worsening event, missing data will be imputed by the last observation carried forward (LOCF) approach.

- For all other reasons without 6MWD measurement, the LOCF approach will be used for imputation.

For missing 6MWD measures beyond Week 48, the missing data will not be imputed, and all analyses will be based on the observed cases.

8.3.3 Missing Data Handling for Other Efficacy Assessments

Similar to 6MWD, analogous rules will be used for the main analyses of Borg dyspnea score and WHO FC. For subjects whose Borg dyspnea score or WHO FC at visits up to Week 48 or NT-proBNP values up to Week 36 are missing, the value will be imputed as follows:

Borg dyspnea score:

- For those subjects who withdrew early due to death, are too ill to perform 6MWT, or have no Borg dyspnea score due to clinical worsening event, the Borg dyspnea score is set to the worst score of 10.
- For missing data occurred at visits prior to death or clinical worsening event, missing data will be imputed by the LOCF approach.
- For all other withdrawals, the LOCF approach will be used for imputation.

For missing Borg dyspnea score at visits beyond Week 48, the missing data will not be imputed, and all analyses will be based on the observed case.

WHO FC:

- For those subjects who withdrew early due to death or have no WHO FC due to a clinical worsening event, the WHO FC is set to the worst value of class IV.
- For missing data occurred at visits prior to death or clinical worsening event, missing data will be imputed by the LOCF approach.
- For all other withdrawals, the LOCF approach will be used for imputation.

For missing WHO FC at visits beyond Week 48, the missing data will not be imputed, and all analyses will be based on the observed case.

NT-proBNP:

- For NT-proBNP, the missing value at visits up to Week 36 will be imputed using the LOCF approach.
- Subjects with missing Baseline NT-proBNP values, the Baseline measure will not be imputed, and these subjects will be excluded from the analyses of the NT-proBNP.

- Subjects with NT-proBNP values reported below the lower limit of quantification, half of the lower limit of quantification will be used for summary and analysis. For example, if the result is reported as '<2.4 pmol/L', a numeric value of 2.4/2=1.2 pmol/L will be used.

The missing values at visits beyond Week 36 will not be imputed and all analyses will be based on the observed cases.

Hemodynamics:
Missing values for hemodynamic parameters will not be imputed. The summary and analyses will be based on the observed cases.

8.4 MULTIPLE COMPARISONS AND MULTIPLICITY

Experimental wise Type I error rate will be controlled at no greater than 0.05 (for 2-sided hypotheses). The study will include an interim analysis for efficacy when 75% of the pre-specified total adjudicated events have occurred. The primary efficacy endpoint will be tested at an interim analysis with an alpha level of 0.020 (2-sided) and at the final analysis at an alpha of 0.044 (2-sided) with the overall Type I error rate controlled at 0.05. Efficacy boundaries for early stopping of the study are calculated based on the O'Brien-Fleming alpha-spending function.

The effect of treatment will be formally tested on the following 3 key secondary efficacy endpoints:

- Change from Baseline in 6MWD at Week 24
- Change from Baseline in NT-proBNP at Week 24
- Change from Baseline in combined 6MWD/Borg dyspnea score at Week 24

In order to control the Type I error rate, the hierarchical (fixed-sequence) test procedure will be used. The p-value for the change from Baseline in 6MWD at Week 24 will be tested at a 2-sided Type I error rate of 0.05. The subsequent tests for change from Baseline in NT-proBNP at Week 24 and then the change from Baseline in combined 6MWD/Borg dyspnea score at Week 24 will be tested only if the preceding test is statistically significant.

The statistical tests for other secondary endpoints below are considered exploratory and no multiplicity adjustment will be applied. For data collected beyond the specified week (eg, Week 48 for 6MWD, Borg score, WHO FC; Week 24 for RHC hemodynamics; and Week 36 for NT-proBNP), descriptive summaries will be provided with no statistical testing.

- 6MWD at all time points prior to Week 48 (other than Week 24)
- Borg dyspnea score at visits prior to Week 48
- WHO FC at visits prior to Week 48
- RHC hemodynamics at Week 24
- NT-proBNP at all time points prior to Week 36 (other than Week 24)

8.5 DERIVED AND TRANSFORMED DATA

Time to Clinical Worsening will be derived as follows:

Parameter	Scenario	Formula	Status
Time to Clinical Worsening (weeks)	Subjects with clinical worsening event reported during the study that is adjudicated/confirmed	= (Worsening date – Randomization date)/7 Note: for subjects with clinical worsening due to worsening 6MWD, the clinical worsening date is date of the second/confirmatory 6MWT	0 (event)
	Subjects who died during the study	= (Death date – Randomization date)/7	0 (event)
	Subjects with clinical worsening event reported during the study that is adjudicated as not meeting the clinical worsening event criteria by the adjudication committee	For analysis of investigator reported clinical worsening event: = (Worsening date – Randomization date)/7 For analysis of adjudicated clinical worsening event: = (Last assessment date – Randomization date)/7	0 (event) 1 (censored)
	Subjects without clinical worsening event during the study	= (Last assessment date – Randomization date)/7	1 (censored)
	Subjects discontinued from the study prematurely that did not have a clinical worsening event	= (Last assessment date – Randomization date)/7	1 (censored)

For subjects with clinical worsening due to the decrease from Baseline in 6MWD, confirmatory 6MWT should be conducted. The event time is based on the date of the

confirmatory 6MWT. As a sensitivity analysis, the event time based on the date of the first reported 6MWT will also be performed.

Hemodynamic parameters will be derived as follows:

Parameter	Formula
Cardiac index in L/min/m^2	= cardiac output (CO) Fick / body surface area (BSA)
Systemic vascular resistance (SVR) in dynes*sec/cm^5	=80 * (systemic arterial pressure mean [SAPm] – right atrial pressure mean [RAPm]) / CO Fick
SVR index (SVRI) in dynes*sec/cm^5/m^2	=80 * (SAPm – RAPm) / cardiac index
Pulmonary vascular resistance (PVR) in dynes*sec/cm^5	=80 * (Pulmonary artery pressure mean [PAPm] – Pulmonary capillary wedge pressure mean [PCWPm]) / CO Fick
PVR Index (PVRI) in dynes*sec/cm^5/m^2	=80 * (PAPm – PCWPm) / cardiac index

Electrocardiogram parameters will be derived as follows:

Parameter	Formula
QTc (Bazett)	$= QT \Big/ \sqrt{\frac{60}{HR}}$
QTc (Fridericia)	$= QT \Big/ \sqrt[3]{\frac{60}{HR}}$

8.6 ASSESSMENT WINDOWS

8.6.1 Assessment Windows for Scheduled Visits

The study protocol included visit windows of +/− 7 or 14 days. However, for any data summarized by scheduled visit, an analysis visit window (proposed in the table below) will be used. The scheduled visits, as recorded on the eCRFs, and the corresponding target days and study day intervals are specified in Table 8-1. The analysis visit window will be derived based on the information specified in Table 8-1.

Table 8-1 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
ECGs and hemodynamics:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 24	169	148 ≤ Study Day ≤190
Clinical laboratory assessments and NT-proBNP:		
Baseline	1	Study Day ≤1 (prior to the fist dose)
Week 12	85	2< Study Day ≤127
Week 24	169	127< Study Day ≤211
Week 36	253	211< Study Day ≤337
Week 60	421	337< Study Day ≤505
Weeks 84, 108, etc	589, 757, etc	(Target Study Day ±84 days)
6MWT, WHO FC, and vital signs:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	15≤ Study Day ≤43
Week 8	57	43< Study Day ≤71
Week 12	85	71< Study Day ≤127
Week 24	169	127< Study Day ≤211
Week 36	253	211< Study Day ≤295
Weeks 48, 60, etc	337, 421, etc	(Target Study Day ±42 days)

Note: Study Day = (Assessment Date) - (First Dosing Date) + 1

8.6.2 Multiple Evaluations within the Same Analysis Window

After all the observations have been slotted based on the table above, if there are multiple valid observations for an assessment within an assigned analysis visit window, only 1 of these observations will be used for summary statistics and analyses. The observation to be used is determined using the following hierarchy (in decreasing order):

- The observation closest to the target study day
- The later observation, if 2 observations are equally close to the target study day

For missing values prior to Week 48 where the LOCF algorithm is applied, it is always the last valid observation on treatment carried forward, even though this might not be the observation obtained by the above hierarchy and used in the summaries by visit window.

9 STUDY POPULATION

Detailed definitions for analysis populations (ITT, Per-Protocol, and Safety Populations) are provided in Section 6. Unless otherwise specified, all efficacy analyses will be performed on the ITT Population and all safety analyses will be based on the Safety Population. In the ITT Population, the treatment assignment is based on the assignment upon randomization. In the Safety Population, the treatment assignment is based on the actual treatment the subject received. Study population will be summarized by the treatment group in the ITT population and overall.

The comparability between the 2 treatment groups will be checked for demographic and Baseline characteristics. The p-values from Fisher's exact test (for discrete variables), group t-test, or Wilcoxon rank sum test (for continuous variables) will be included in summaries but are not intended to be used to test formal hypotheses. For these comparisons, missing or unknown values will be excluded from the calculations.

9.1 SUBJECT ACCOUNTABILITY

All subjects' disposition information will be listed, including the study population the subjects belong to, whether or not subjects completed the study drug treatment, reason study drug was stopped, whether or not subjects completed at least 24 weeks of study assessments, primary reason for not completing 24 weeks of assessments, whether or not subjects completed the study, reason for not completing the study, and whether or not subjects rolled over to the open-label extension study (TDE-PH-311).

The listing of subject accountability will include dates of informed consent, randomization, first study drug dose, last study drug dose, last dose week, and last assessment week. Whether subjects received study drug; whether subjects completed the Weeks 4, 8, 12, and 24 assessments, and every 12-week follow-up assessment thereafter; study drug termination status; and study discontinuation status will be summarized by treatment group and overall.

Information regarding whether each subject is included in each analysis population (see Section 6) will be listed. If a subject is not included in a particular analysis population, the reason for exclusion will be noted on the listing. Also noted on the listing will be the

randomized treatment assignment and the actual treatment subjects have received. The summary will include the frequency and percentage of all subjects in each analysis population by treatment group and overall.

All stratification information used in the random assignment of subjects to treatment group (from the central randomization database) will be listed, including date and time of randomization, background PAH therapy, Baseline walk distance category, whether or not the treatment is unblinded, and if so, date/time of blind break. For observations where any stratification information has been corrected, both the original and corrected information will be listed. Background PAH therapy and Baseline walk distance used for randomization stratification will be summarized by treatment group and compared using Fisher's exact test or Wilcoxon rank sum test, as appropriate.

9.2 PROTOCOL DEVIATIONS

The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment and a list of any specific entry criteria not met. Entry criteria violations will be summarized by treatment group and overall.

Additional protocol deviations will be documented throughout the study, and protocol deviations and their severity categories will be summarized by treatment group and included in the data listing.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATIONS

9.3.1 Demographics

All demographic data will be listed for all subjects, including country, age at randomization, sex, ethnicity, race, weight, height, and Body Mass Index (BMI). Age, age category (<65 years versus ≥65 years), sex, ethnicity, race, weight, height, and BMI will be summarized by treatment group. The summary will include p-values (2-sided) from Fisher's exact test (for age category, sex, ethnicity, and each race), group t-test, or Wilcoxon rank sum test (for age, weight, height, and BMI) comparing treatment groups.

9.3.2 Medical History and PAH History

All significant past or ongoing medical conditions will be listed for all subjects. The listing will include the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for each condition listed. These medical conditions will be summarized by PT within each SOC by treatment group.

Information related to subjects' PAH history will be listed. The listing will include the date of initial PAH diagnosis, time since diagnosis at randomization, and etiology of PAH. A separate listing will include details of the subjects' background PAH therapy (eg, PDE5-I/sGC stimulator or ERA use).

Time since diagnosis and etiology of PAH will be summarized by treatment group. The summary will include p-values (2-sided) from Fisher's exact test (for etiology of PAH) or Wilcoxon rank sum test (for time since diagnosis) comparing treatment groups.

Background PAH therapy at Baseline will be summarized by treatment group. The summary will include the number and percentage of each PAH therapy use, time on background PAH therapy, and the total daily dose of the background PAH therapy.

9.3.3 Concomitant Medications

All concomitant medications specified on the eCRF will be mapped to a standard term using the WHO Drug Dictionary (WHO-DD).

The standard name and verbatim term of all concomitant medications will be listed for all subjects. This listing will include the date started (or indication that drug was ongoing at randomization), date discontinued (or indication that drug was ongoing at end of study), and the condition treated/indications. If a subject received no medications, this will be indicated in the listing. The summary of concomitant medications will include the frequency and percentage of subjects in each treatment group receiving each drug (by coded standard name). Concomitant medications ongoing at Baseline and those added during the study will be summarized separately.

Changes to ERA, PDE5-I, and sGC stimulator dosing that are collected separately from the concomitant medication page will be listed.

10 EFFICACY ANALYSES

Except where otherwise noted, all efficacy analyses will only be performed on the ITT Population (see Section 6).

10.1 PRIMARY EFFICACY MEASURES

10.1.1 Time to Clinical Worsening

Clinical worsening is defined as the occurrence of any of the following:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or
  - Lung or hearg transplantation; or
  - Atrial septostomy
- Initiation of an inhaled or infused prostacyclin for the treatment of worsening PAH
- Disease progression (all criteria required):
  - A decrease in 6MWD of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by 2 6MWTs performed on different days.
  - Worsening of PAH symptoms, which must include either:
    - An increase in FC since Baseline or
    - Appearance or worsening of symptoms of right heart failure since Baseline
- Unsatisfactory long-term clinical response (all criteria required)
  - Randomized to receive study drug for at least 24 weeks
  - A decrease from Baseline in 6MWD at Week 24 and beyond at 2 consecutive visits on different days
  - Sustained WHO FC III or IV symptoms for at least 24 weeks, consecutively

10.1.1.1 Hypothesis

The study is designed to determine the efficacy of UT-15C compared with placebo in subjects with PAH. The null hypothesis tested for the primary endpoint of time to adjudicated clinical worsening is that there is no difference in hazard ratio in the time to clinical worsening of PAH when treated with UT-15C compared with placebo:

$$H_0: hazard\ ratio = 1$$

The 2-sided alternative hypothesis is that there is a difference:

$$H_a: hazard\ ratio \neq 1$$

Due to the alpha spending on interim analysis, for the final analysis, the significance level for the primary efficacy analysis of time to adjudicated clinical worsening is 0.044.

10.1.1.2 Primary Efficacy Analyses

Data on the Clinical Worsening Assessment page of the eCRF will be used in determining clinical worsening status. Investigator-reported clinical worsening events will be reported directly from the eCRF data, regardless of the outcome of the adjudication committee review. An independent adjudication committee will be utilized to adjudicate all investigator-reported clinical worsening events. Adjudicated clinical worsening events will be reported using data received from the adjudication committee.

Subjects who discontinue study drug for reasons other than clinical worsening will be censored at the time of discontinuation of the study drug. Non-fatal clinical worsening events that occur more than 7 days after permanent study drug discontinuation will not be included in the summary and analysis of clinical worsening events. However, all deaths within the study follow-up period (30 days after the last study drug dose) will be included as clinical worsening events. Time to clinical worsening will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan-Meier curves. A tabular summary of this analysis will include the number of subjects at risk (sample size), estimated median duration, and a 95% confidence interval for the median duration for each treatment group.

For the primary efficacy analysis of time to adjudicated clinical worsening, the log-rank test adjusted for the type of background therapy (PDE5-I or sGC stimulator versus ERA) and the Baseline 6MWD (≤350 meters versus >350 meters) will be used to calculate the p-value for treatment differences in the ITT Population.

The SAS Procedure LIFETEST will be used. The pseudo SAS statements are listed below:

```
proc lifetest;
     time TimeToWorsening*Censor_Status(1);
     strata BGTX B_6MWD / group=Treatment test=all;
run;
```

where BGTX variable denotes the background therapy and B_6MWD denotes the Baseline 6MWD category (≤350 meters versus >350 meters).

10.1.1.3 Sensitivity and Subgroup Analyses

The primary efficacy analysis of time to adjudicated clinical worsening events will also be provided for the Per-protocol Population.

The following sensitivity analyses will be performed:

- For all subjects who drop out from the study early, they are considered as having a clinical worsening event. Time to event will be calculated from randomization to subject's discontinuation date.
- For all subjects who drop out from the study early due to AEs, they are considered as having a clinical worsening event. Time to event is calculated from randomization to subject's study discontinuation date.

The time from randomization to clinical worsening will also be compared between treatment groups using a Cox proportional-hazards regression model, adjusting for Baseline 6MWD category ((≤350 meters versus >350 meters) and background PAH therapy (as a categorical variable: PDE5-I/sGC stimulator or ERA). Hazard ratio and its 95% confidence interval will be calculated. SAS Procedure PHREG will be used and the pseudo SAS statements are listed below:

```
proc phreg;
  Model TimeToWorsening*Censor_Status(1) = treatment;
  Strata BGTX B_6MWD / risklimits ties=efron;
run;
```

where BGTX variable denotes the background therapy and B_6MWD denotes the Baseline 6MWD category≤350 meters versus >350.

Subgroup analyses will be performed on the following factors: background PAH therapy, PAH etiology, Baseline WHO FC, age group (<65 years versus ≥65 years), Baseline 6MWD category, sex (male versus female), maximum dose achieved (<9 mg versus ≥9mg total daily dose) , and geographic region as specified in Section 8.2. The estimated hazard ratio between the active and placebo groups from this model will be calculated and displayed along with its 95% confidence interval on the summary and analysis table and plot.

Since clinical worsening is a composite endpoint, the following components of this composite endpoint will also be summarized and analyzed with the same approach as the composite endpoint:

- Time to death (all causes) during the study
- Time to hospitalization due to worsening PAH

In addition, time to death (all causes) by the end of the study will also be summarized and analyzed. For time to death by the end of the study analysis, the vital status for all subjects will also be collected throughout the study to the completion of the last subject in the study including subjects who discontinued the study early and subjects who rolled over to the extension study (TDE-PH-311).

For each of the above time-to-event variables, the assumption of proportional hazards will be assessed using a log-log survival plot, with log of time as the x-axis and log negative log survival distribution function (SDF) as the y-axis. This plot will be reviewed to assess if the curves were parallel and thus the proportional hazards assumption for treatment is met. In additional, the proportional hazards assumptions will also be checked by using the time * treatment or time*covariate interactions in the model. The PROC LIFETEST procedure in SAS will be used to calculate the survival function estimates for the plots. If the non-proportional hazard model is suggested, the alternative approaches, such as an extension of the Cox regression model, may be explored.

10.2 KEY SECONDARY EFFICACY MEASURES

The effect of treatment will be formally tested on the following 3 secondary endpoints:

- Change from Baseline in 6MWD at Week 24
- Change from Baseline in NT-proBNP at Week 24
- Change from Baseline in combined 6MWD/Borg dyspnea score at Week 24

The tests for these 3 key secondary efficacy endpoints will be hierarchal with a fixed sequence approach as described in Section 8.4.

10.2.1 Analysis of 6MWD Including Change from Baseline to Week 24

The efficacy endpoint of 6MWD assesses if UT-15C increases the distance traversed in the 6MWT at Week 24 over placebo in subjects with PAH. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2$$

where μ1 and μ2 are the mean change from Baseline in 6MWD of the UT-15C and placebo treatment groups, respectively.

A longitudinal data analysis using mixed model repeated measurement (MMRM) will be performed to estimate the treatment difference in change in 6MWD at Week 24. The MMRM model will be based on the observed measures up to Week 24 and will include the changes from Baseline in 6MWD as the dependent variable; treatment, week, treatment by week interaction, and background PAH therapy as fixed effects; and Baseline 6MWD as a covariate. An unstructured variance/covariance structure shared across treatment groups will be used to model the within-subject errors and Kenward-Roger method will be used for calculating the denominator degree of freedom. The appropriate contrasts will be constructed in order to estimate treatment effect at Week 24 and other visits. The pseudo SAS codes are as following:

```
proc mixed;
  class trt01p(ref='PLACEBO') BGTX avisitn usubjid;
  model DistC = trt01p BGTX avisitn trt01p*avisitn
```

```
        Dist0/ddfm = kr;
    repeated avisitn /type= un subject = usubjid;
    lsmeans trt01p*avisitn/diff;
    estimate "at Week 24" trt01p 1 -1
                          trt01p*avisitn  0 0 0 1
                                          0 0 0 -1/cl;
run;
```

where BGTX is background PAH therapy, DistC is the change from Baseline in 6MWD, and Dist0 is the Baseline measure of the 6MWD.

From the same model, the contrasts will also be constructed to estimate the treatment effects at Weeks 4, 8, 12 assessments.

All 6MWT data will be listed for all subjects. For each scheduled assessment, this listing will include the date test was performed (or date test was intended to be performed if subject is unable to attempt the test), start time of the test, nominal time point, total distance walked (in meters), Borg dyspnea score, whether subject received oxygen during the test, and any circumstances that adversely affected the walk (if any), including reason for not attempting test (if any).

For each visit (Week 24 for key secondary efficacy endpoint, and other visits for exploratory efficacy endpoints), the effect of UT-15C versus placebo on 6MWD will also be evaluated using non-parametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (Koch 1990, Koch 1998, Stokes 2000). Specifically, a Cochran-Mantel-Haenszel mean score test will be used on the standardized mid-ranks (ie, overall rank divided by the number of ranks +1, or "modified ridit" scores) of the residuals from an ordinary least squares regression with change from Baseline in 6MWD at Week 24 as a linear function of background therapy (as a categorical variable: PDE5-I/sGC stimulator or ERA) and distance walked at Baseline (as a continuous variable). This methodology will be carried out as follows:

1. Walk distances obtained subsequent to study drug termination or unblinding will be excluded (as described in Section 8).
2. Calculating ranks by background PAH therapy subgroup. The pseudo SAS codes are as following:

```
proc rank nplus1 ties=mean out=ranks;
   by BGTX;
   var DistC Dist0;
run;
```

where BGTX is background PAH therapy, DistC is the change from Baseline in 6MWD, and Dist0 is the Baseline measure of the 6MWD.

3. Separate linear regression models for each background PAH therapy group will be fit using the rank values generated above. The pseudo SAS codes are as following:

```
proc reg data=ranks noprint;
   by BGTX;
   model DistC=Dist0;
   output out=residual r=resid;
run;
```

where BGTX is background PAH therapy, DistC is the rank value of the change from Baseline in 6MWD, and Dist0 is the rank value of the Baseline measure of the 6MWD.

4. A stratified mean score test, using the values of the residuals as scores, compares the treatment groups. Cochran-Mantel-Haenszel mean score statistic and p-value will be calculated using the NOPRINT and CMH2 options in the TABLES statement of the FREQ procedure of SAS. The actual stratification used to randomize each subject will be used. The pseudo SAS codes are as following:

```
proc freq;
   tables BGTX*treatment*resid / noprint cmh2;
run;
```

where BGTX is background PAH therapy, Treatment indicates the randomized treatment group, and Resid is the residuals obtained from the above linear regression models.

In addition to the p-value from the non-parametric analyses of covariance described above, the Wilcoxon rank sum test and the Hodges-Lehmann estimate of median difference (as an estimate of location shift between 2 treatment groups for the placebo-controlled treatment effect) will be provided. The Wilcoxon rank sum test and the Hodges-Lehmann estimate can be obtained through the following pseudo SAS codes:

```
proc npar1way hl Wilcoxon;
     class treatment;
     var DistC;
      run;
```

where DistC is the change from Baseline in 6MWD at a specific visit.

The least square mean, least square mean difference, and p-value for treatment group comparison will also be provided using the parametric method — analysis of covariance model where the change from Baseline in 6MWD is the dependent variable, treatment and background PAH therapy are fixed effects, and Baseline 6MWD is a covariate.

10.2.1.1 Sensitivity and Sub-group Analyses

This methodology for key secondary efficacy analysis of change in 6MWD at Week 24 using MMRM will also be carried out with data up to Week 48 included in the model. The treatment effects at weeks 36 and 48 will be estimated.

With non-parametric analysis of covariance method, in order to analyze walk distances at each scheduled assessment, values for missing or excluded assessments up to Week 48 will be imputed according to rules described under "Missing data handling for 6MWD" in Section 8.3. Missing values beyond Week 48 will not be imputed. The visits beyond Week 48 will only be summarized using the observed values.

To further support the robustness and assess the sensitivity of efficacy analysis of change in 6MWD at Week 24, the above MMRM method will be repeated using each of the following modifications:

- MMRM model with the Per-Protocol Population
- MMRM model with only subjects achieve total daily dose ≥ 9 mg.

Analyses using non-parametric analysis of covariance will be repeated using each of the following modifications (as data permit):

- Wth the Per-Protocol Population
- Using only the observed values without imputation
- Including data collected after termination of the study drug
- Analyses will be carried out within PAH etiology categories
- Analyses will be carried out within Baseline WHO FC categories
- Analyses will be carried out within PAH background therapy categories
- Analyses will be carried out within Baseline 6MWD categories (≤350 meters versus >350 meters)

- Analyses will be carried out within geographic regions
- Analyses will be carried out within sex
- Analyses will be carried out within age group (<65 years versus ≥65 years)
- Analyses will be carried out by study drug dose at Week 24 (total daily dose <9 mg and ≥9 mg)
- Analyses will be carried out within UT-15C dose quartile at Week 24
- Plot of 6MWD at Week 24 by UT-15C dose

10.2.2 NT-proBNP

The efficacy endpoint of NT-proBNP assesses if UT-15C decreases the level of NT-proBNP at Week 24 over placebo in subjects with PAH. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2$$

Where μ_1 and μ_2 are the mean change from Baseline for log-transformed data in NT-proBNP of the UT-15C and placebo treatment groups, respectively, and the change from Baseline is calculated as log (value at week 24) – log (value at Baseline).

The NT-proBNP values will be listed for all subjects. The values and their respective changes from Baseline will be summarized for each assessment. The summary will also include the geometric mean and geometric standard deviation. The difference between treatment groups for the change from Baseline for log-transformed data at each assessment at Week 24 will be tested using an analysis of covariance model with change from Baseline for log-transformed data in NT-proBNP as the dependent variable, treatment as a fixed effect, and Baseline NT-proBNP as a covariate. The pseudo SAS codes are as following:

```
proc mixed;
   class treatment;
   model BNP_C=Treatment BNP_B;
run;
```

where BNP_C is the change from Baseline for log-transformed data in NT-proBNP at a specific visit and BNP_B is the NT-proBNP for log-transformed data at Baseline.

Subjects who do not have a valid NT-proBNP measurement at Baseline or Week 24 will be excluded from the analysis. Additional analyses will also be performed for the data with imputation where for subjects who do not have NT-proBNP measurements at Week 24, the LOCF imputation will be used.

A longitudinal data analysis using MMRM will also be performed to estimate the treatment difference in changes from Baseline for log-transformed data in NT-proBNP at Week 24. The MMRM will include the change from Baseline for log-transformed data in NT-proBNP as the dependent variable; treatment, week, and treatment by week interaction as fixed effects; and Baseline NT-proBNP for log-transformed data as a covariate. An unstructured variance/covariance structure shared across treatment groups will be used to model the within-subject errors and Kenward-Roger method will be used for calculating the denominator degree of freedom. The appropriate contrasts will be constructed in order to estimate treatment effect at Week 24 and other visits.

NT-proBNP data in observed cases will be descriptively summarized for other visits with measurements.

10.2.3 Combined 6MWD and Borg Dyspnea Score

The intent of the 6MWT is to determine how much exercise subjects can do during the course of carrying out activities of daily living. However, the capacity of subjects to function is determined not only by what they can do when they exert themselves to the fullest, but also by how they feel when they are carrying out their usual activities of daily living. It is therefore important not only to look at the distance traversed during the unencouraged 6MWT, but also the symptoms experienced at the end of the effort. To do so, walk distances and Borg dyspnea scores from the Week 24 6MWT will be simultaneously compared between treatment groups using a nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (analogous to the key secondary analysis methodology for 6MWD at week 24). This methodology will be carried out as follows:

- Standardized mid-ranks of change in walk distance will be calculated as described in Section 10.2.1

- Standardized mid-ranks of change in Borg dyspnea score will be calculated in an analogous manner, but in reverse (descending) order
- The standardized mid-ranks for change in walk distance and for change in Borg dyspnea score will be combined by calculating their arithmetic average
- A Cochran-Mantel-Haenszel mean score test will be carried out on the standardized mid-ranks of these combined ranks in an analogous manner to that described in Section 10.2.1

The treatment distributions of these combined ranks at Week 24 will be displayed graphically using Kaplan-Meier plots. These plots will include the information from the treatment comparison analysis described above.

10.3 OTHER SECONDARY EFFICACY MEASURES

10.3.1 6MWD at Other Visits Except Week 24

The method for analysis of change in 6MWD at other visits up to Week 48 (except Week 24) is the same as for the analysis of 6MWD at Week 24, and it has been described in Section 10.2.1.

The observed values for 6MWD at all visits, including visits beyond Week 48, will be listed and descriptively summarized according to the requirements described in Section 8.

10.3.2 Borg Dyspnea Score

The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT. Scores range from 0 (for the best condition) to 10 or more (for the worst condition). Scores will be listed with the corresponding 6MWT data for each subject. Change from Baseline for visits up to Week 48 will be compared between the 2 treatment groups using non-parametric Hodges-Lehmann estimator and Wilcoxon rank-sum test as well as parametric 2-sample t-test. Values for missing or excluded assessments up to Week 48 will be imputed. For those patients who withdrew early due to death, or a clinical worsening event without Borg dyspnea score measurement at visits up to Week 48, the Borg dyspnea score is set to worst score of 10; for all other withdrawals without Borg measurement, the LOCF method is used for imputation.

The observed values for Borg dyspnea score at all visits, including visits beyond Week 48, will be descriptively summarized according to the requirements described in Section 8.

10.3.3 WHO FC

WHO FC values (ie, class I, II, III, or IV) will be listed for all subjects at each assessment time point. Class I, II, III, or IV will be assigned values 1, 2, 3, 4 for the calculations. The shift from Baseline in WHO FC (categorized as Improved, No Change, and Deteriorated) for visits up to Week 48 will be compared between the 2 treatment groups using Fisher's exact test. The change from Baseline in WHO FC for visits up to Week 48 will be compared between the 2 treatment groups using the non-parametric Hodges-Lehmann estimator and Wilcoxon rank-sum test. Values for missing or excluded assessments up to Week 48 will be imputed. For those patients who withdrew early due to death or a clinical worsening event without WHO FC measurement at visits up to Week 48, the WHO FC is set to the worst class value of IV; for all other withdrawals without WHO FC measurement, the LOCF method is used for imputation.

10.3.4 NT-proBNP

NT-proBNP at weeks 12 and 36 will be analysed in the same way as described in Section 10.2.2. In addition, NT-proBNP at weeks 12, 24, and 36 will also be analysed with LOCF imputation for missing data. NT-proBNP at other timepoints will only be summarized.

10.3.5 Hemodynamic Parameters

Values of all hemodynamic parameters obtained as part of the optional hemodynamic study (heart rate, systemic arterial pressure systolic [SAPs], systemic arterial pressure diastolic [SAPd], systemic arterial pressure mean [SAPm], pulmonary artery pressure systolic [PAPs], pulmonary artery pressure diastolic [PAPd], pulmonary artery pressure mean [PAPm], right atrial pressure mean [RAPm], pulmonary capillary wedge pressure mean [PCWPm], systemic arterial oxygen saturation [SaO_2], mixed venous oxygen saturation [SvO_2], CO Thermodilution, CO Fick, and BSA) will be listed for all subjects with hemodynamic measures. Additional hemodynamic parameters, including cardiac index, SVR, SVRI, PVR, and PVRI, will be derived according to the formulas described in Section 8.5.

The values and their respective changes from Baseline to Week 24 will be summarized by treatment group for each hemodynamic parameter. The difference between treatment groups for the change from Baseline to Week 24 will be tested using analysis of covariance, with change from Baseline as the dependent variable, treatment as the fixed effect, and Baseline measure as the covariate. The results from the non-parametric Wilcoxon rank-sum test will also be provided. The analyses will be based on the observed cases, and no imputation will be performed for the missing values.

10.4 EXPLORATORY ANALYSIS

10.4.1 The low risk-profile analysis

Risk categories will be defined and the shift in risk categories will be analyzed according to the method defined in Weatherald et al (Weatherald 2018). The number and percentage of subjects with a low risk profile at Week 24 or other time points will be calculated and a treatment group comparison will be performed.

10.4.2 Optional Evaluation of Biomarkers

The optional evaluation of biomarkers will be specified in a separate document and not covered in this SAP.

10.4.3 Optional Evaluation of Pharmacogenomics

The optional evaluation of pharmacogenomics will be specified in a separate document and not covered in this SAP.

11 HEALTH OUTCOMES

11.1 QUALITY OF LIFE MEASURES

Quality of life was not assessed during this study.

11.2 RESOURCE UTILIZATION MEASURES

All details for all hospitalizations will be listed. Number of hospitalizations, number of hospitalizations for PAH, total duration of hospitalization, and total duration of hospitalization for PAH will be summarized for each treatment group.

12 SAFETY ANALYSES

All safety analyses will be performed only on the Safety Population (see Section 6).

12.1 EXTENT OF EXPOSURE

All study drug dosing will be listed for all subjects. The listing will include initial dose and date of this initial dose, dose and date of each change, and whether each change applied to the morning, afternoon, or evening doses. Dosing at Weeks 4, 8, 12, 24, and every 12-week follow-up assessment will be summarized for subjects still receiving study drug at each of these assessments. A summary by treatment group of maximum study drug dose and overall duration of exposure will be included. The study drug dosing and exposure by the use of background PAH therapy will be provided in a separate summary.

In addition, a summary table will be provided for study drug treatment compliance for the first 24 weeks by treatment group. The summary will include the number and percent of days subjects are dosed and total study drug consumed for first 24 weeks.

12.2 ADVERSE EVENTS

All AEs will be coded using MedDRA and will be listed by treatment group, including all the details on the eCRF page plus an indicator of whether the event was treatment emergent. The AE listings will include the AE verbatim term and its corresponding PT and SOC.

The AE summary tables will be limited to include only treatment-emergent AEs and will be summarized for each treatment group. Treatment-emergent AEs are those AEs with an onset date equal to or after the start date of the study drug. The non-treatment emergent AEs (the AEs that occur after signing the informed consent form, but before receiving study drug, will be listed but will not be included in summary tables.

All summaries will include the number and percentage of subjects experiencing each type of event based on PT and the total number of each type of event, in order of overall frequency and/or SOC. Serious AEs and non-serious AEs will be summarized by PT.

Maximum level of seriousness and intensity occurring during the treatment phase for each AE will be summarized separately and by causality (probable or possible versus not related).

Considering the potential imbalance in treatment exposure, the total number of AEs and the AE rate will be calculated and summarized. The AE rate will be calculated as the total number of AEs divided by the total patient years per treatment group.

Separate listings and summary tables will be provided for all serious adverse events (SAEs), AEs leading to the discontinuation of the study drug, and all deaths during the study.

12.3 DEATHS

Information for all subjects who die during the study period from randomization to the end of study (including 30 days after the last study drug dosing) will be listed. The number and percent of subjects who die will be summarized by treatment group.

In addition, the information for vital status, including alive/death, last known date subject is alive, or date of death at the study closure, will also be listed.

Death information is also analysed as an efficacy endpoint as described in Sections 10.1.1.2 and 10.1.1.3.

12.4 PREGNANCIES

Pregnancy test results for female subjects will be listed.

12.5 CLINICAL LABORATORY EVALUATIONS

Blood samples will be taken at Baseline; Weeks 12, 24, 36; and every 24 weeks thereafter during the study. All samples will be sent to a central laboratory for evaluation of clinical chemistry and hematology. Urine samples collected at screening and study drug termination visit will be collected and sent to a central laboratory for urinalysis.

12.5.1 Clinical Chemistry

The following clinical chemistry parameters will be evaluated by the central laboratory:

Parameter	Units
Sodium	mmol/L
Potassium	mmol/L
Chloride	mmol/L
Bicarbonate	mmol/L

Parameter	Units
Albumin	g/L
Blood urea nitrogen (BUN)	mmol/dL
Total bilirubin	umol/dL
Indirect bilirubin	umol/dL
Direct bilirubin	umol/dL
Alkaline phosphatase	U/L
Alanine aminotrasferase (ALT/SGPT)	U/L
Aspartate aminotransferase (AST/SGOT)	U/L
Gamma-glutamyl transferase (GGT)	U/L
Creatinine	umol/L
Thyroid stimulating hormone (TSH)	mIU/L
Thyroxine (T4; free)	pmol/L

Values that are "high" or "low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L." All parameters will be listed for all subjects and assessments, along with their respective "high/low" flags.

Values of these parameters at each assessment and their corresponding changes from Baseline will be descriptively summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who had "low," "normal," or "high" Baseline values, then subsequently had "low," "normal," or "high" follow-up values at each assessment will be presented in a shift summary.

12.5.2 Hematology

The following hematology parameters will be evaluated by the central laboratory:

Parameter	Units
Red blood cell (RBC) count	10^6/uL
Hemoglobin	g/dL
Hematocrit	%
Platelet count	10^3/uL
White blood cell (WBC) count	10^3/uL

Values that are "high" or "low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L." All parameters will be listed for all subjects and assessments, along with their respective "high/low" flags.

Values of these parameters at each assessment, and their corresponding changes from Baseline will be descriptively summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who had "low," "normal," or "high" Baseline values, then subsequently had "low," "normal," or "high" follow-up values at each assessment will be presented in a shift summary.

12.5.3 Urinalysis

All urinalysis information will be listed for all subjects and assessments. The presence of protein and blood in the urine will be categorically summarized by treatment group.

12.6 ELECTROCARDIOGRAMS

All ECG assessments will be listed for all subjects. This listing will include the heart rate, QT interval, QTc interval (calculated using formulas by both Bazett and Fridericia as described in Section 8.5), PR interval, QRS duration, whether there were clinically significant changes from Screening visit, whether abnormalities were present, and details and comments on any abnormalities. The ECG results at each assessment and changes at Week 24 will be descriptively summarized by treatment group. In addition, for QTc interval calculated using both the Bazett and Fridericia methods, the number and percent of subjects with values ≥500 msec and the number and percent of subjects with changes of <30 msec, 30 to <60 msec, and ≥60 msec will be presented by treatment group.

12.7 VITAL SIGNS

All vital sign assessments will be listed for all subjects. This listing will include weight, heart rate, systolic and diastolic blood pressure, and respiration rate. The vital sign results at each assessment and changes for each post-Baseline assessment will be descriptively summarized by treatment group.

12.8 DISEASE-RELATED EVENTS

All disease-related events occurring during the study will be listed for all subjects. Overall frequency of each type of event will be summarized by treatment group.

13 PHARMACOKINETICS

No pharmacokinetic measures will be assessed in this study.

14 REFERENCES

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15 APPENDICES

15.1 INCLUSION AND EXCLUSION CRITERIA

A subject is eligible for inclusion in this study if all of the following criteria apply:

1. The subject voluntarily gives informed consent to participate in the study.
2. The subject is 18 to 75 years of age (inclusive) at Screening (ie, date of providing written informed consent).
3. Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months). Women of childbearing potential must practice true abstinence from intercourse when it is in line with their preferred and usual lifestyle, or use 2 different forms of highly effective contraception for the duration of the study and for at least 30 days after discontinuing study medication. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device (IUD), or (4) partner vasectomy. For women of childbearing potential, a negative urine pregnancy test is required at Screening and Baseline prior to initiating study medication.
4. The subject, if male, must use a condom during the length of the study, and for at least 48 hours after discontinuing study medication.
5. The subject has a diagnosis of symptomatic idiopathic or heritable PAH, PAH associated with connective tissue disorder (CTD), PAH associated with human immunodeficience virus (HIV) infection, PAH associated with repaired congenital systemic-to-pulmonary shunt (at least 1 year since repair with respect to the date of providing informed consent), or PAH associated with appetite suppressant or toxin use.
6. The subject, if known to be positive for HIV infection, has a CD4 lymphocyte count of at least 200 cells/mm^3 assessed at Screening and is receiving current standard of care anti-retroviral or other effective medication for treatment of HIV infection.
7. The subject must have a Baseline 6MWD greater than or equal to 150 meters, in the absence of a concurrent injury, illness (other than PAH or a PAH related condition), or other confounding factor including, but not limited to, use of an aid for ambulation (eg, use of a cane or walker) or connection to a non-portable machine, that would prevent the accurate assessment of the subject's exercise capacity.
8. The subject must be optimally treated with conventional pulmonary hypertension therapy (eg, oral vasodilators, oxygen, digoxin, diuretics, anticoagulants as deemed appropriate by the Investigator) with no additions, discontinuations, or dose changes for a minimum of 10 days prior to randomization. The exceptions are the discontinuation or dose changes of anticoagulants and/or dose change of diuretics.

9. The subject must have been receiving a PAH-approved oral monotherapy at a minimum dose that complies with the approved prescribing information for the product for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization. The subject who previously received 2 PAH-approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or an sGC stimulator) will be eligible provided they received these medications concomitantly for less than or equal to 90 days cumulatively. The subject must have taken only 1 PAH-approved therapy for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization.
10. The subject has previously undergone a cardiac catheterization within 3 years prior to the start of Screening, or during the Screening period, and the most recent assessment has documented a PAPm of at least 25 mmHg, a PCWP (or in the event a PCWP cannot be reliably obtained, a left ventricular end-diastolic pressure [LVEDP]) less than or equal to 15 mmHg, and absence of unrepaired congenital heart disease (other than patent foramen ovale [PFO]). In the event that a reliable PCWP or LVEDP is unobtainable during cardiac catheterization, subjects with clinically normal left heart function and absence of clinically relevant mitral valve disease on echocardiography are eligible for enrollment.
11. The subject has undergone echocardiography with evidence of clinically normal left systolic and diastolic ventricular function and absence of any clinically significant left sided heart disease (eg, mitral valve disease). Subjects with clinically insignificant left ventricular diastolic dysfunction due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) are eligible.
12. The subject has a previous ventilation perfusion lung scan, and/or high resolution computerized tomography scan of the chest, and/or pulmonary angiography that are consistent with the diagnosis of PAH (eg, low probability of pulmonary embolism; absence of major perfusion defects).
13. The subject has pulmonary function tests conducted within 6 months before Screening or during the Screening period to confirm the following:
    a. Total lung capacity (TLC) is at least 60% (predicted value) assessed by either whole body plethysmography or helium dilution or nitrogen washout technique
    b. Forced expiratory volume at 1 second (FEV_1) of at least 50% (predicted value)
14. In the opinion of the Principal Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing, and likely to be cooperative with protocol requirements, including attending all study visits.

A subject is not eligible for inclusion in this study if any of the following criteria apply:

1. The subject is pregnant or lactating.
2. The subject has previously received UT-15C.
3. The subject has received a prostacyclin (except if used during acute vasoreactivity testing) within 30 days prior to randomization or had previous intolerance or

significant lack of efficacy to any prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to titrate that therapy effectively.

4. The subject has had any background conventional therapies for PAH added, removed, or dose adjusted (including but not limited to oxygen, vasodilators, diuretics, digoxin, anticoagulants) within 10 days prior to randomization. The exceptions are removal or dose adjustments of anticoagulants and/or dose adjustments of diuretics.
5. The subject has received their first dose of a PAH-approved therapy less than 30 days prior to randomization, has had their PAH-approved oral monotherapy dose changed within 10 days prior to randomization, the subject discontinued any PAH-approved therapy within 30 days prior to Screening, or the subject previously received 2 PAH approved oral therapies (specifically, a PDE5-I, an ERA, or an sGC stimulator) concomitantly for more than 90 days cumulatively.
6. The subject has any disease associated with PAH other than CTD, HIV infection, repaired (for at least 1 year) congenital systemic-to-pulmonary shunt, PAH associated with appetite suppressant/toxin use (eg, portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc), or has had an atrial septostomy.
7. The subject has a current diagnosis of uncontrolled sleep apnea as defined by their physician.
8. The subject has a history of ischemic heart disease, including a previous myocardial infarction or symptomatic coronary artery disease within 6 months prior to Screening or a history of left sided myocardial disease as evidenced by a mean PCWP (or a LVEDP) greater than 15 mmHg or left ventricular ejection fraction less than 40%, as assessed by either multigated angiogram (MUGA), angiography, or echocardiography.
9. The subject has uncontrolled systemic hypertension, as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
10. The subject has ALT or AST levels at least greater than 3 times the upper limit of normal, clinically significant liver disease/dysfunction, or known Child-Pugh Class C hepatic disease at Screening.
11. The subject has any other disease or condition that would interfere with the interpretation of study assessments.
12. The subject has a musculoskeletal disorder (eg, arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (eg, cane or walker), or any disease that is likely to limit ambulation, or is connected to a machine that is not portable.
13. The subject has an unstable psychiatric condition or is mentally incapable of understanding the objectives, nature, or consequences of the study, or has any condition which in the Investigator's opinion would constitute an unacceptable risk to the subject's safety.
14. The subject is receiving an investigational drug, has an investigational device in place, or has participated in an investigational drug or device study within 30 days prior to Screening.
15. The subject has chronic renal insufficiency, as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 μmol/L) or the requirement for dialysis.

16. Subjects must not have 3 or more of the following left ventricular disease/dysfunction risk factors:
    i. Body Mass Index (BMI) ≥30 kg/m^2
    ii. History of essential hypertension
    iii. Diabetes mellitus (any type)
    iv. Historical evidence of significant coronary disease established by any one of the following: history of myocardial infarction or percutaneous coronary intervention or angiographic evidence of coronary artery disease (>50% stenosis in at least 1 coronary artery), positive stress test with imaging, previous coronary artery bypass graft, stable angina

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