Document Type:	Statistical Analysis Plan	**Protocol / Study No.:**	RIN-PH-201
First Draft Date:	10 APR 2018	**Total Number of Pages including Appendices:**	39
Finalization Date:	27 FEB 2019		
Classification:	Confidential	**Version:**	2.0

Title:

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

Author: [redacted]

TABLE OF CONTENTS

Table of In-Text Tables

ABBREVIATIONS AND DEFINITIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BOCF	Baseline Observation Carried Forward
CHP	Chronic Hypersensitivity Pneumonitis
CPFE	Combined Pulmonary Fibrosis and Emphysema
CSR	Clinical study report
CT	Computed Tomography
CTD	Connective tissue disease
DLCO	Lung diffusion capacity
DMC	Data Monitoring Committee
DSP	Distance saturation product
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early termination
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HR	Heart rate
ICF	Informed consent form
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
ITT	Intent-to-treat
LOCF	Last observation carried forward
LRCF	Last rank carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurement
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAPm	Pulmonary artery pressure mean
PCWP	Pulmonary capillary wedge pressure
PFT	Pulmonary function test
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease

P-R	Time between P wave and beginning of QRS complex in electrocardiography
PT	Preferred Term
PVR	Pulmonary vascular resistance
Q-T	Electrocardiographic interval from beginning of QRS complex to end of the T wave
QTc	QT interval corrected for heart rate
QRS	Electrocardiographic wave interval
RHC	Right heart catheterization
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SpO_2	Saturation of Peripheral Capillary Oxygenation
TLC	Total lung capacity
WHO-DD	World Health Organization Drug Dictionary
WU	Wood Units

1 PREFACE

This plan provides further details of the planned analyses for the RIN-PH-201 study as presented in the study protocol. This plan, based on the original RIN-PH-201 study protocol dated 21 Oct 2015 and the subsequent study protocol amendments (latest version study protocol amendment 3 dated 15 February 2017), provides further details of the planned analyses stated in the study protocol as well as any 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 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the safety and efficacy of inhaled treprostinil in subjects with Pulmonary Hypertension (PH) associated with Interstitial Lung Disease (ILD), including Combined Pulmonary Fibrosis and Emphysema (CPFE).

2.1 PRIMARY ENDPOINT

The primary endpoint is the change in 6-Minute Walk Distance (6MWD) measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

The secondary endpoints are:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints are:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD from Baseline to Week 8
3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:

   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
5. Change in distance saturation product (DSP) from Baseline to Week 16

Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They will be specified in separate documents and not covered in this statistical analysis plan.

2.4 SAFETY ENDPOINTS

Safety endpoints will be used to evaluate safety based on the following assessments:

1. Adverse events (AEs)
2. Oxygenation:
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO2])
   b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
   a. Forced expiratory volume in 1 second (FEV1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalization due to a cardiopulmonary indication.
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

3 STUDY DESIGN

This is a multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study. Subject eligibility will be based on the inclusion and exclusion criteria described in Section 4 of the protocol. Approximately 314 eligible subjects will be randomized to study

treatments (inhaled treprostinil or placebo) in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤350 meters versus >350 meters).

Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (randomization and first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo Screening assessments. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline pulmonary function tests (PFTs) and 6-Minute Walk Test (6MWT) used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Baseline Visit: The Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments, be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6MWT used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Treatment Phase: The Treatment phase consists of 5 study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit; at least 24 hours after the Week 15 Visit [final study visit/early termination {ET}]). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

4 SEQUENCE OF PLANNED ANALYSES

Interim Safety Analyses

Interim safety analyses are intended to be performed according to the Data Monitoring Committee (DMC) Charter. In particular, interim safety analyses are planned following the enrollment of approximately 25%, 50%, and 75% of subjects in the study, or at least annually (whichever is sooner). 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 the blinded study data during this process. Interim efficacy analyses are not planned in this study.

Dry-run Analysis Prior to Database Lock (Soft Lock)

At the completion of the study enrollment and prior to the database lock, a dry-run analysis is planned. This dry-run analysis utilizes a dummy randomization schedule in a blinded fashion. The purpose of the dry-run analysis is to verify programming of the analysis data sets and the planned tables, listings, and figures, and to identify any data issues. Programming and data issues identified through the dry-run process will be resolved prior to the database lock and study unblinding.

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 the clinical database after unblinding. However, any changes that are deemed necessary, after unblinding, will be clearly documented in the CSR.

5 SAMPLE SIZE CONSIDERATIONS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD, assuming a standard deviation of 75 meters.

The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

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 ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses will be performed on this ITT population, unless otherwise specified.

The Safety population is defined as all subjects enrolled into the study who received at least 1 dose of study drug. All Safety population subjects will be counted in the group corresponding to the study drug received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

The Per-protocol population will include all subjects in 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.

7 INTERIM ANALYSES

There is no interim efficacy analysis for this study.

A DMC will be established for the study including physicians knowledgeable in the treatment of PH 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 as outlined in the DMC Charter. 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. The details regarding the interim safety analysis will be included in a separate statistical analysis plan.

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 or the nominal time point 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 are not to 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 whenever practical, categories of discrete variables will be ordered and labelled as they appear in the eCRF, and all categories represented on the case report form will be included in summaries, even when they do not apply to any subjects in the study.

Unless otherwise specified, all statistical tests will be 2-sided at alpha level 0.05. All statistical calculations will be completed using SAS® Version 9.4 or above.

8.1 COVARIATES

The primary efficacy analyses of change in 6MWD at Week 16 will be adjusted for Baseline 6MWD (as a continuous variable). For sensitivity analyses of the primary efficacy endpoints and the secondary/exploratory endpoints with continuous variables, the baseline measure will always be the covariate.

8.2 EXAMINATION OF SUBGROUPS

For primary efficacy endpoints of change in 6MWD at Week 16, subgroup analyses will be performed. These subgroups will include:

- Etiology of ILD (Idiopathic Interstitial Pneumonia [IIP], Chronic Hypersensitivity Pneumonitis [CHP], Occupational, CPFE, Connective Tissue Disease [CTD], and Other)
- Baseline walk categories (≤350 meters versus >350 meters, ≤ median baseline 6MWD versus > median baseline 6MWD)
- ILD disease severity as measured by Baseline DLCO (<40% predicted versus ≥40% predicted)

- Sex (male versus female)
- Pulmonary Vascular Resistance (PVR) (<4 versus ≥4 Wood Units [WU])
- Age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths)

No Type 1 error adjustments will be performed for these subgroup analyses.

8.3 PREMATURE DISCONTINUATION AND MISSING DATA

8.3.1 Missing Data Handling for 6MWD

For the analysis of 6MWD, subjects may not have completed the treatment with study drug prior to the Week 16 visit for the following reasons: death, progressive disease, AE, withdrawal of consent by the subject, protocol violation, 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 withdrawal from the study. In addition, subjects still receiving study drug may be too critically ill to perform the 6MWT, resulting in missing data for that assessment.

Every effort should be made to complete all scheduled study assessments for all randomized subjects. Although attempts will be made to continue to collect data after termination of study drug, these data are being collected for sensitivity analyses and descriptive purposes only. Assessments performed after treatment unblinding or more than 24 hours after the last dose of study drug will not be included in the main analyses of peak 6MWD.

For subjects whose peak 6MWD measures at Week 4, Week 8, Week 12, or Week 16 are missing, the missing value will be imputed as described in Table 8-1.

Table 8-1 Imputation Rules for Peak 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening event	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Last (peak) Observation Carried Forward (LOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test.

For subjects whose trough 6MWD measures at Week 15 are missing, the missing values will be imputed as described in Table 8-2.

Table 8-2 Imputation Rules for Trough 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Baseline Observation Carried Forward (BOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test, BOCF, Baseline observation carried forward.

8.3.2 Missing Data Handling for Other Efficacy Assessments

For the secondary endpoints of NT-proBNP, the missing value at Week 16 will be imputed using LOCF. If the NT-proBNP measure at Baseline is missing, the change from Baseline will not be calculated. The subject will not be included in the analyses.

For exploratory endpoints of SGRQ, biomarkers, and DSP, the missing values will not be imputed, and all analyses will be based on the observed cases.

8.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The primary efficacy endpoint of change in 6MWD measured at peak exposure from Baseline to Week 16 will be tested at alpha level 0.05. If the primary efficacy endpoint is statistically significant at alpha level 0.05, the statistical tests for secondary efficacy endpoints will be performed.

To control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed-sequence) testing procedure. The change from Baseline in peak 6MWD at Week 12 will be tested at a 2-sided Type 1 error rate of 0.05. The subsequent tests for change from Baseline in NT-proBNP at Week 16, and then the change from Baseline in trough 6MWD at Week 15, will be tested sequentially only if the preceding test is statistically significant.

8.5 DERIVED AND TRANSFORMED DATA

Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:

- Hospitalization due to a cardiopulmonary indication
- Decrease in 6MWD >15% from Baseline directly related to disease under study at 2 consecutive visits and at least 24 hours apart
- Death (all causes)
- Lung transplantation

Time to clinical worsening is calculated as described in Table 8-3.

Table 8-3 Derivation of Time to Clinical Worsening

Parameter	Scenario	Formula	Status
Time to clinical worsening (weeks)	Subjects with clinical worsening event reported	= (Worsening date – Randomization date +1)/7	0 (event)
	Subjects who died during the study	= (Death date – Randomization date +1)/7	0 (event)
	Subjects without clinical worsening event during the study	= (Last assessment date – Randomization date +1)/7	1 (censored)
	Subjects discontinued from the study prematurely	= (Last assessment date – Randomization date +1)/7	1 (censored)

For subjects with clinical worsening due to decrease from Baseline in 6MWD, a confirmatory 6MWT should be conducted. The event time is based on the date of the confirmatory 6MWT. If the confirmatory 6MWT is not conducted, the event time is then based on the date of the first 6MWT.

Distance Saturation Product (DSP) is calculated as follows:

Parameter	Formula
DSP (m%)	= (Distance walked in meters) x (Lowest oxygen saturation recorded during the 6MWT)

Abbreviations: 6MWT, 6-Minute Walk Test; DSP, Distance Saturation Product.

Adjustments to the QT intervals will be calculated as follows:

Parameter	Formula
QTc (Bazett)	$= Q\text{-}T/\sqrt{60/HR}$
QTc (Fridericia)	$= Q\text{-}T/\sqrt[3]{60/HR}$

Abbreviations: HR, Heart rate; QTc, Q-T interval corrected for heart rate; Q-T, Electrocardiographic interval from beginning of QRS complex to end of the T wave.

8.6 ASSESSMENT WINDOWS

For any data summarized by scheduled visit, an analysis visit window will be used. The scheduled visits, as recorded on the eCRFs, and the corresponding target days and study day intervals are specified in Table 8-4. The analysis visit window will be derived based on the information specified in Table 8-4.

In the protocol, the visit window for Week 4, Week 8, Week 12, and Week 16 is ±5 days and the visit window for the Week 15 visit is ±5 days and at least 24 hours prior to Week 16 6MWT. In order to allow slotting of discontinuation visits and visits outside the planned schedule, the visit windows have been expanded for analysis purposes for Week 4, Week 8, Week 12, and Week 16. The nominal study visit identified as Week 15 in the eCRF will be used for the Week 15 visit provided it is at least 24 hours prior to Week 16 6MWT or there is no Week 16 visit.

Table 8-4 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
ECGs, SGRQ:		
Baseline	1	Study Day ≤1 (prior to the date of the first dose)
Week 16	113	1 < Study Day
PFTs, Clinical laboratory assessments and NT-proBNP:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 8	57	1 < Study Day ≤ 71
Week 16	113	99 < Study Day
Peak 6MWT:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 16	113	99 < Study Day
Trough 6MWT:		
Week 15	106	Nominal study visit and at least 24 hours prior to Week 16 6MWT or no Week 16 visit
Vital signs, Pulse oximetry:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 15	106	Nominal study visit and at least 24 hours prior to Week 16 6MWT or no Week 16 visit
Week 16	113	99 < Study Day

Note: Study Day = (Assessment Date) − (First Dosing Date) +1
Abbreviations: 6MWT, 6-Minute Walk Test; ECG, Electrocardiogram; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PFT, Pulmonary function test.

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 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

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.

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) or Group t-test or Wilcoxon rank sum test (for continuous variables) will be included on 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 by individual subject number, including the analysis population the subjects belong to, premature study drug discontinuation status, primary reason for premature study drug discontinuation, premature study discontinuation status, primary reason for premature study discontinuation, number of days on the study drug, and enrollment in the open label extension study (RIN-PH-202).

The listing of subject accountability will include the dates of informed consent and randomization, the first study drug dose, last study drug dose, and last assessment dates and times, and the last dose and assessment weeks. Whether subjects received the study drug, whether subjects completed the Weeks 4, 8, 12, 15, 16 assessments, and study discontinuation status will be summarized.

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.

The 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 and Baseline 6MWD category (≤350 meters versus >350 meters). Status of the treatment blind, and if broken, date/time of blind broken will be listed. The number of subjects in each stratum will be summarized by treatment group and overall.

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, whether all eligibility criteria were met (Yes/No), and a list of any specific entry criteria not met. This listing will also include the protocol version that the subject was enrolled under. Entry criteria violations will be summarized by treatment group and overall.

Additional protocol deviations will be documented throughout the study. All deviations will be reviewed by the clinical team prior to database lock and those that might affect subject safety or efficacy outcomes will be considered 'Major'. All other deviations will be classified as 'Minor'. Protocol deviations will be listed, including the date of the deviation, the type of deviation, the severity of the deviation (Major/Minor), and a description of the deviation. The protocol deviations will also be summarized by treatment group and overall.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

All demographic data will be listed for all subjects, including assessment date, date of birth, country, age, sex, ethnicity, race, weight, height, and body mass index (BMI). Age, age category (<65 years of age, 65 to <80 years of age, and ≥80 years of age), sex, ethnicity, race,

height, weight, and BMI will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher's exact test (for age category, sex, ethnicity, and race) and group t-test or Wilcoxon rank sum test (for age, weight, height, and BMI) comparing treatment groups.

9.3.2 Baseline Characteristics

Baseline characteristics will include the Baseline 6MWD, Baseline NT-proBNP, and hemodynamic parameters. Hemodynamic parameters, measured by the right heart catheterization (RHC), will include PVR, pulmonary artery pressure mean (PAPm), pulmonary capillary wedge pressure (PCWP), and details concerning vasodilator testing will be listed and summarized.

9.3.3 Medical History and PH-ILD 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, and whether the condition is ongoing at Randomization. These medical conditions will be summarized by PT within each SOC.

Information related to subjects' PH-ILD history will be listed. The listing will include the date of initial PH diagnosis, years since PH diagnosis, etiology of ILD (including IIP subcategory), date of confirmatory computed tomography (CT) scan, whether ILD diagnosis confirmed with a lung biopsy, and if so, the date of lung biopsy.

The current ILD diagnosis (ILD category) and IIP subcategory, time since PH diagnosis, and whether ILD diagnosis was confirmed via lung biopsy will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher's exact test (for current ILD diagnosis) or Wilcoxon rank sum test (for time since diagnosis) comparing treatment groups.

9.3.4 Concomitant Medications

All concomitant medications specified on the eCRF will be mapped to a standard name using the World Health Organization 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(s) treated/indication(s). If a subject received no medications, this will be indicated on the listing. Summary of concomitant medications present at Baseline and summary of concomitant medications added during the study will include the frequency and percentage of subjects in each treatment group receiving each drug (by coded standard name).

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 Primary Efficacy Analyses

10.1.1.1 Hypothesis

The primary efficacy endpoint of peak 6MWD assesses if inhaled treprostinil will increase the distance traversed in the peak 6MWT at Week 16 over placebo in subjects with PH-ILD. 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 median change from Baseline in 6MWD of the inhaled treprostinil and placebo treatment groups, respectively.

10.1.1.2 Primary Efficacy Analysis

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, last treatment dose, hours from last treatment dose to 6MWT start, if walk was attempted, total distance walked (in meters), whether subject received oxygen during the test, amount of supplemental oxygen, and any circumstances that adversely affected the walk (if any) including reason for not

attempting test (if any). The trough 6MWT measure will also be indicated. In addition, a listing of 6MWD with imputed values will be included for both peak and trough 6MWD data.

For the primary efficacy analysis, the effect of inhaled treprostinil versus placebo on change in peak 6MWD at Week 16 will be evaluated via analysis of covariance (ANCOVA). Change from Baseline in peak 6MWD is the dependent variable, and treatment and Baseline 6MWD are covariates in this ANCOVA model. Least squares means and standard errors for each treatment group, the least squares mean difference and its standard error, as well as a 95% confidence interval for the treatment group difference and p-value for treatment group comparison will be calculated from the ANCOVA model. This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. The LOCF algorithm will be applied.
4. ANCOVA will be conducted based on the pseudo SAS code:

```
proc glm;
  class Treatment;
  model DistC = Treatment Dist0;
run;
```

where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.

If the ANCOVA assumptions are violated, the primary efficacy analysis will be based on 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 peak 6MWD at Week 16 as a linear function of distance walked at Baseline (as a continuous variable). This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. Calculate ranks. The pseudo SAS code is as follows:

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

   where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.
4. Linear regression model will be fit using the rank values generated above. The pseudo SAS code is as follows:

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

   where DistC is the rank value of the change from Baseline in peak 6MWD at Week 16 and Dist0 is the rank value of the baseline measure of the 6MWD.
5. A 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 pseudo SAS code is as follows:

   ```
   proc freq data=residual;
     tables Treatment*Resid / noprint cmh2;
   run;
   ```

   where Treatment indicates the randomized treatment group, and Resid represents the residuals obtained from the above linear regression models.

In addition to the p-value from the non-parametric method 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 code:

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

where DistC is the change from Baseline in peak 6MWD at Week 16.

10.1.1.3 Sensitivity and Subgroup Analyses

In order to analyze walk distances at each scheduled assessment, values for missing or excluded assessments up to and including Week 16 will be imputed according to rules described in Section 8.3.1.

To further support the robustness and assess the sensitivity of the primary efficacy analysis of change in peak 6MWD at Week 16 (provided that the primary analysis yields significant results), the above non-parametric and parametric analyses and summaries will be repeated using each of the following modifications (as data permit):

- The Per-protocol population will be used instead of the ITT population
- Missing data imputation using the LOCF method (based on peak values)
- Missing data imputation using the last rank carried forward (LRCF) method (based on peak values) (O'Brien 2005)
- Using only the observed values without imputation
- Including data collected after termination of the study drug
- ITT population excluding subjects with a reported exacerbation within 3 days of the Week 16 peak 6MWT measure
- Stratified by ILD etiology categories (IIP, CHP, Occupational, CPFE, and Other)
- Stratified by Baseline 6MWD categories (≤350 meters versus >350 meters, ≤median baseline 6MWD versus > median baseline 6MWD)
- Stratified by Baseline DLCO percent predicted (<40% versus ≥40%)
- Stratified by Baseline pulmonary vascular resistance (PVR) (<4 versus ≥4 WU)
- Stratified by sex (male versus female)
- Stratified by age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Stratified by study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths).

A longitudinal data analysis using mixed model repeated measurement (MMRM) will also be performed to estimate the treatment difference in change in peak 6MWD at Week 16. The MMRM will include the change from Baseline in peak 6MWD as the dependent variable, treatment, week, and treatment by week interaction 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.

An additional sensitivity analysis will be performed for percent change from Baseline to Week 16 in peak 6MWD using the same approach as the primary analysis method where the percent change from Baseline is calculated as

$$\frac{\text{peak 6MWD at Week 16} - \text{Baseline 6MWD}}{\text{Baseline 6MWD}} \text{X } (100\%).$$

In addition, the impact of Baseline hemodynamics and Baseline PFTs, including PVR, PAPm, PCWP, FEV_1, FVC, TLC, and DLCO as continuous variables, on peak 6MWD, will be explored using the regression approach.

10.2 SECONDARY EFFICACY MEASURES

Secondary efficacy endpoints include the following:

- Change in peak 6MWD from Baseline to Week 12
- Change in plasma concentration of NT-proBNP from Baseline to Week 16
- Change in trough 6MWD from Baseline to Week 15

As specified in Section 8.4 above, the hierarchical (fixed-sequence) testing procedure will be employed to control the overall alpha level at 0.05.

10.2.1 Change in Peak 6MWD at Week 12

The methodology for primary efficacy analysis of change in peak 6MWD at Week 16 will also be carried out for the Week 12 assessment, as described above in Section 10.1.1.2.

10.2.2 Change in NT-proBNP at Week 16

The efficacy endpoint of change in NT-proBNP assesses if inhaled treprostinil decreases the level of NT-proBNP at Week 16 over placebo in subjects with PH-ILD. 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 median change from Baseline to Week 16 in NT-proBNP of the inhaled treprostinil and placebo treatment groups, respectively.

The NT-proBNP values will be listed for all subjects, including the nominal time point, collection date/time, normal range and "High/Low" flag. The values and their respective changes from Baseline will be summarized for each assessment. The difference between treatment groups for the change from Baseline to Week 16 will be tested using the analysis of covariance with change from Baseline in NT-proBNP as the dependent variable, treatment as the fixed effect, and Baseline NT-proBNP as the covariate. The pseudo SAS code is as follows:

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

where BNP_C is the change from Baseline to Week 16 in NT-proBNP and BNP_B is the NT-proBNP at Baseline.

If assumptions (normality and equal variance) for the parametric test are violated, the nonparametric Wilcoxon rank-sum test will be used. For subjects who do not have NT-proBNP measurements at Week 16, the LOCF imputation will be used. The analyses will also be performed for the data without imputation for the missing measures.

As an exploratory analysis, the NT-proBNP at Week 8 will be analysed using the same method as the NT-proBNP at Week 16.

10.2.3 Change in Trough 6MWD at Week 15

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the change in trough 6MWD from Baseline to Week 15. Missing trough 6MWD will be imputed as described in Table 8-2 in Section 8.3.1. The analysis will be repeated to include only subjects with trough 6MWD at Week 15 (ie, missing trough 6MWD at Week 15 is not imputed).

10.3 EXPLORATORY EFFICACY MEASURES

Exploratory efficacy endpoints include the following parameters:

- Change in peak 6MWD from Baseline to Week 4
- Change in peak 6MWD from Baseline to Week 8
- Change in quality of life as measured by SGRQ from Baseline to Week 16
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:
  a. Hospitalization due to a cardiopulmonary indication
  b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  c. Death (all causes)
  d. Lung transplantation
- Change in DSP from Baseline to Week 16

10.3.1 Change in Peak 6MWD at Weeks 4 and 8

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the assessments obtained at Week 4 and Week 8.

10.3.2 Change in SGRQ at Week 16

The responses to the SGRQ questionnaire at Baseline and Week 16 will be converted to the Total score and 3 domain scores according to the SGRQ manual (Jones 2002). Scores for Total and each domain will range from 0 to 100, with higher scores indicating more limitations. Both individual item responses as well as calculated scores will be listed. The change from Baseline for the Total and 3 domain scores (Symptoms, Activity, and Impacts) will be calculated.

The Total score and for the 3 domain scores as well as their changes from Baseline will be summarized by treatment group using descriptive statistics.

For the Total score and each of the 3 domain scores, treatment differences (inhaled treprostinil vs. placebo) will be tested by using analysis of covariance with change from Baseline as the dependent variable, treatment as a fixed effect, and baseline score as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model Score_C=Treatment Score_B;
run;
```

where Score_C is the change from Baseline in Total score or each of the 3 domain scores and Score_B is the corresponding score at Baseline.

10.3.3 Time to Clinical Worsening

- Data on the clinical worsening assessment page of the eCRF will be used to determine clinical worsening status. Investigator-reported clinical worsening events including the date (study day) of the event, category of the clinical worsening event, Baseline 6MWD, first 6MWT details, and second 6MWT details will be listed. The time to clinical worsening will be calculated according to the rules described in Table 8-3 in Section 8.5.

The number and percentage of subjects with any clinical worsening and with each category of clinical worsening will be summarized by treatment group. 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. The log-rank test, adjusted for Baseline 6MWD category, 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 B_6MWD / group = Treatment test=all;
run;
```

where B_6MWD denotes the categorical Baseline 6MWD variable (≤350 meters versus >350 meters).

In addition, the Cox proportional hazards model will be fit to obtain the hazard ratio and its associated 95% confidence interval. The model will include treatment and Baseline 6MWD as explanatory variables. The SAS procedure PHREG will be used. The pseudo SAS statements are listed below:

```
proc phreg;
  class Treatment;
  model TimeToWorsening*Censor_Status(1) = Treatment Dist0
        / risklimits alpha=0.05 ties=efron;
  assess var=Dist0 ph;
run;
```

where Dist0 denotes the Baseline 6MWD variable (continuous). If it is determined that the proportional hazards assumption does not hold for Baseline 6MWD, a stratified analysis will be conducted. The above SAS code will be amended to remove Dist0 from the model statement and add the 'strata B_6MWD;' statement.

If the proportional hazards assumption does not hold for the Cox model, the restricted mean survival time (RMST) and its associated standard error will be calculated for each treatment group at Week 16 (Royston 2013). A 95% confidence interval will be constructed for the difference in RMST between the 2 treatment groups at Week 16.

10.3.4 Change in DSP

The DSP will be calculated, and DSP results will be included in the data listing for pulse oximetry. DSP values and their respective changes from Baseline to Week 16 will be summarized by treatment group. The difference between treatment groups for the change from Baseline to Week 16 will be tested using analysis of covariance with change from Baseline in DSP as the dependent variable, treatment as a fixed effect, and Baseline DSP measure as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model DSP_C=Treatment DSP_B;
run;
```

where DSP_C is the change from Baseline to Week 16 in DSP (m%) and DSP_B is DSP at Baseline.

In addition, the DSP at Week 4, Week 8, and Week 12 will each be analyzed in the same way as the DSP at Week 16.

11 HEALTH OUTCOMES

11.1 QUALITY OF LIFE MEASURES

Quality of life was assessed using SGRQ. The analyses of SGRQ are described in Section 10.3.2.

11.2 RESOURCE UTILIZATION MEASURES

Hospitalizations and hospitalizations related to cardiopulmonary indications are collected during the study. The analysis is discussed in Section 12.6.2.

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 (number of breaths for each session and number of breaths for the day) and date of this initial dose and dose and date of each subsequent dose change. Dosing at Weeks 4, 8, 12, 15, and 16 will be summarized for subjects still receiving study drug at each of these assessments. The summary will include both the numeric summaries and the categorical summaries for number of breaths per session as well as the number of breaths per day. If study drug is dosed differently across different sessions on the same day, the maximum number of breaths is used for summarization. Summary of overall duration of exposure will be included as well as the

final dose (breath/session) and the maximum study drug dose (breath/session) reached for each subject (numerically and categorically).

For study treatment compliance, the number and percentage of days with dose >0 breaths will be calculated and summarized.

12.2 ADVERSE EVENTS

All AEs will be coded to the appropriate PT and SOC using MedDRA. AEs will be listed by treatment group including all details recorded on the eCRF 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 summaries will be limited to include only treatment-emergent AEs. Treatment-emergent AEs are those AEs with onset date equal to or after the start date of the study drug. The non-treatment-emergent AEs (the AEs occur after signing the informed consent form but before receiving study drug) will be listed but not included in summary tables.

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

The total number of AEs and the AE rates will be calculated and summarized for each display, as appropriate. The AE rate will be calculated as the total number of AEs divided by the total patient years of exposure to study drug per treatment group.

Adverse events possibly or probably related to study drug will be summarized. An AE summary by severity (mild, moderate, and severe) will also be provided.

Separate listings and summary tables will be provided for all SAEs, AEs leading to the discontinuation of study drug, and all deaths during the study (if data permit). For listing of deaths, information for all subjects who die during the study period from the randomization to the end of study (including 30 days after the last study treatment dosing) will be included.

12.3 OXYGENATION

Oxygenation is measured by pulse oximetry (SpO_2 and supplemental oxygen requirement [L/min]) during each 6MWT. At each 6MWT, pulse oximetry (for SpO_2) will be measured at pre-walk, during walk, and post-walk. During walk, the lowest SpO_2 will be recorded. All pulse oximetry results along with the collection date/time (study day) will be listed. Heart rate will be listed for pre-walk and post-walk only.

The SpO_2 will be summarized by treatment group, visit, and time point (pre-walk, during walk, and post-walk). The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from Baseline calculations, the measurements pre-walk, during walk, and post walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk, during walk, and post-walk at Baseline.

In addition, for each time point at each visit, the number and percentage of subjects with SpO_2 or lowest SpO_2 <80%, ≥80 to <88, and ≥88%, and with SpO_2 dropping ≥10% during walk and/or post-walk from pre-walk will be summarized by treatment group.

At each visit, supplemental oxygen requirements will be collected at rest and during 6MWT. These data will be listed, including visit, 6MWT date/time, and oxygen use at rest and during walk. The number and percentage of subjects requiring supplemental oxygen use at rest and during the 6MWT will also be summarized by the treatment group. Supplemental oxygen level at rest at each visit and the corresponding changes from Baseline will be summarized by treatment group.

Heart rate will be summarized by treatment group, by time point (pre-walk and post-walk) and visit. The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from baseline calculations, the measurements pre-walk and post-walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk and post-walk at Baseline.

12.4 PULMONARY FUNCTION TESTS

The PFT parameters include:

- Forced expiratory volume in 1 second (FEV_1)
- Forced vital capacity (FVC)
- Total lung capacity (TLC)
- Lung diffusion capacity (DLCO)

Only pre-bronchodilator values will be recorded on eCRF and will be listed. All PFT parameters and their change from baseline values will be summarized by treatment group and visit.

For FEV_1 results, the number and percentage of subjects with FEV_1 decreasing more than 20% from Baseline at any post-Baseline Visit will be summarized by treatment group.

12.5 CLINICAL LABORATORY EVALUATIONS

Blood samples will be taken at Screening and/or Baseline, Week 8, and Week 16. All samples will be sent to a central laboratory for evaluation of clinical chemistry and hematology.

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
Bicarbonate	mmol/L
Chloride	mmol/L
Total bilirubin	umol/dL
Alkaline phosphatase	U/L
Alanine aminotrasferase	U/L
Aspartate aminotransferase	U/L
Urea nitrogen	mmol/dL
Creatinine	umol/L
Calcium	mmol/L
Albumin	g/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," respectively. All parameters will be listed for all subjects and assessments, along with their respective "High/Low" flags.

Values of these parameters at each visit, 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 visit will be presented in a shift summary.

12.5.2 Hematology

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

Parameter	**Units**
Hemoglobin	g/dL
Hematocrit	%
Red blood cell count	10^6/uL
Red blood cell morphology	
White blood cell count	10^3/uL
Platelet 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," respectively. All parameters will be listed for all subjects and assessments, along with their respective "High/Low" flags.

Numeric values of these parameters at each visit and their corresponding changes from Baseline will be summarized by treatment group.

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

12.5.3 Pregnancy Test

Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit. All pregnancy tests will be performed at study sites. Pregnancy status during the study will be listed.

12.6 OTHER SAFETY MEASURES

12.6.1 Electrocardiograms

All ECG assessments will be listed for all subjects. This listing will include the heart rate, the ECG interval from the beginning of QRS complex to end of the T wave (Q-T interval), the QT interval corrected for heart rate (QTc) (calculated using formulas by both Bazett and Fridericia as described in Section 8.4), the time between P wave and beginning of QRS complex in ECG (P-R interval), the electrocardiographic wave (QRS) duration, ECG results (Normal/Abnormal), whether there were clinically significant changes from Screening visit, whether abnormalities were present, and details and comments on any abnormalities. The ECG results at Baseline and changes at Week 16 will be descriptively summarized by treatment group. In addition, for QTc intervals 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 from Screening of <30 msec, 30 to <60 msec, and ≥60 msec will be presented. Additionally, each abnormality will be summarized by number and percentage of subjects reporting at each visit by treatment group.

12.6.2 Hospitalizations

Details for all hospitalizations will be listed. Number of hospitalizations for cardiopulmonary indications and total duration of hospitalization for cardiopulmonary indications will be summarized for each treatment group as well as overall number of hospitalizations and total duration regardless of indication.

12.6.3 Vital Signs

All vital sign assessments will be listed for all subjects. This listing will include height, weight, body mass index (BMI), heart rate, systolic and diastolic blood pressures, respiratory

rate, and temperature. The vital sign results at each assessment and changes for each post-Baseline assessment will be descriptively summarized by treatment group.

12.6.4 Exacerbations of Underlying Lung Disease

Exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Number of subjects with exacerbation of underlying lung disease will be summarized for each treatment group and included in the overall AE summary table. A listing of these events will also be provided.

13 PHARMACOKINETICS

No pharmacokinetic measures will be assessed in this study.

14 REFERENCES

Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respiratory J.* 2002;19:398–404.

Koch GG, Carr GJ, Amara IA, et al. Categorical data analysis. In Berry DA ed. *Statistical Methodology in the Pharmaceutical Sciences.* New York, NY: Marcel Dekker Inc.; 1990:391–475.

Koch GG, Tangen CM, Jung JW, et al. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. *Stat Med.* 1998;17(15-16):1863–1892.

O'Brien PC, Zhang D, Bailey KR. Semi-parametric and non-parametric methods for clinical trials with incomplete data. *Statist. Med.* 2005;24:341–358.

Royston P, Parmar MKB. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Medical Research Methodology* 2013;13:152.

Stokes ME, Davis CS, Koch GG. *Categorical Data Analysis Using the SAS System.* 2nd Edition. Cary, NC: SAS Institute Inc.; 2000.

15 LIST OF TABLES, LISTINGS AND FIGURES

15.1 LIST OF TABLES

Table Number	Table Title
14.1.1	Summary of Subject Accountability
14.1.2	Summary of Analysis Population Information
14.1.3	Summary of Demographic Data
14.1.4	Summary of Baseline Characteristics
14.1.5	Summary of PH-ILD History
14.1.6.1	Summary of Entry Criteria Violations
14.1.6.2	Summary of Protocol Deviations
14.1.7	Summary of Randomization Information
14.1.8	Summary of Medical History
14.1.9	Summary of Concomitant Medications Ongoing at Baseline
14.1.10	Summary of Concomitant Medications Added During the Study
14.1.11	Summary of Study Drug Dosing and Exposure
14.1.12	Summary of Study Drug Treatment Compliance
14.2.1.1	Summary and Analysis of Peak 6MWD (meter) at Week 16 – Primary Efficacy Endpoint
14.2.1.2	Summary and Analysis of Peak 6MWD (meter) at Week 16 – Per Protocol Population
14.2.1.3	Summary and Analysis of Peak 6MWD (meter) at Week 16 with LOCF Imputation for Missing Data
14.2.1.4	Summary and Analysis of Peak 6MWD (meter) at Week 16 with LRCF Imputation for Missing Data
14.2.1.5	Summary and Analysis of Peak 6MWD (meter) at Week 16 with No Imputation for Missing Data
14.2.1.6	Summary and Analysis of Peak 6MWD (meter) at Week 16 Including Data Collected after Termination of Study Drug
14.2.1.7	Summary and Analysis of Peak 6MWD (meter) at Week 16 Excluding Subjects with a Reported Exacerbation within 3 Days of the Week 16 6MWD Measure
14.2.1.8	Analysis of Peak 6MWD (meter) at Week 16 Using Mixed Model Repeated Measurement (MMRM)
14.2.1.9	Summary and Analysis of Percent Change from Baseline to Week 16 in Peak 6MWD
14.2.1.10	Summary and Analysis of Peak 6-Minute Walk Distance (meter) at Week 16 by ILD Etiology Category
14.2.1.11.1	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Baseline 6MWD Category (≤350 meters versus >350 meters)
14.2.1.11.2	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Baseline 6MWD Category (≤baseline median meters versus>baseline median meters)

Table Number	Table Title
14.2.1.12	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Baseline DLCO Percent Predicted
14.2.1.13	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Baseline PVR
14.2.1.14	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Sex
14.2.1.15	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Age Group
14.2.1.16	Summary and Analysis of Peak 6MWD (meter) at Week 16 by Study Drug Dose at Week 16
14.2.1.17	Summary of Effects of Baseline Hemodynamics and Baseline PFTs on Peak 6MWD by Week
14.2.2.1	Summary and Analysis of Peak 6MWD (meter) at Week 12 – Secondary Efficacy Endpoint
14.2.2.2	Summary and Analysis of Peak 6MWD (meter) at Weeks 4 and 8
14.2.3.1	Summary and Analysis of NT-proBNP (pg/mL) Data at Week 16 – Secondary Efficacy Endpoint
14.2.3.2	Summary and Analysis of NT-proBNP (pg/mL) Data at Week 16 – with Observed Case
14.2.3.3	Summary and Analysis of NT-proBNP (pg/mL) Data at Week 8
14.2.3.4	Summary and Analysis of NT-proBNP (pg/mL) Data at Week 8 with Observed Case
14.2.4.1	Summary and Analysis of Trough 6MWD (meter) at Week 15 – Secondary Efficacy Endpoint
14.2.4.2	Summary and Analysis of Trough 6MWD (meter) at Week 15 with Observed Case
14.2.5.1	Summary and Analysis of Clinical Worsening Events
14.2.5.2	Summary of Hospitalization Information
14.2.6.1	Summary and Analysis of SGRQ Total Score
14.2.6.2	Summary and Analysis of SGRQ Symptoms Score
14.2.6.3	Summary and Analysis of SGRQ Activity Score
14.2.6.4	Summary and Analysis of SGRQ Impacts Score
14.2.7	Summary and Analysis of Distance Saturation Product (DSP) (m%)
14.3.1.1	Overall Summary of Adverse Events and Exacerbations of Underlying Lung Diseases
14.3.1.2	Summary of Adverse Events by System Organ Class and Preferred Term
14.3.1.3	Summary of Adverse Events by Preferred Term
14.3.1.4	Summary of Deaths
14.3.1.5	Summary of Serious Adverse Events by System Organ Class and Preferred Term
14.3.1.6	Summary of Non-Serious Adverse Events by System Organ Class and Preferred Term
14.3.1.7	Summary of Adverse Events Probably or Possibly Related to Study Drug by System Organ Class and Preferred Term

Table Number	Table Title
14.3.1.8	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug by Preferred Term
14.3.1.9	Summary of Adverse Events by System Organ Class, Preferred Term, and Severity
14.3.1.10	Summary of Adverse Events by Study Drug Dose at AE Onset
14.3.2.1	List of Deaths
14.3.2.2	List of Serious Adverse Events
14.3.4.1	Summary of SpO2 (%) Measured by Pulse Oximetry
14.3.4.2	Categorical Summary of SpO2 (%) Measured by Pulse Oximetry
14.3.4.3	Summary of Heart Rate (beats/min) by Pulse Oximetry
14.3.4.4	Summary of Supplemental Oxygen Use
14.3.4.5	Summary of Supplemental Oxygen (L/min)
14.3.4.6	Summary of Pulmonary Function Test Results
14.3.4.7	Summary of Subjects with ≥20% Decrease in FEV1 from Baseline
14.3.4.8.1	Summary of Laboratory Data – Clinical Chemistry
14.3.4.8.2	Summary of Clinical Chemistry Shift from Baseline
14.3.4.8.3	Summary of Laboratory Data – Hematology
14.3.4.8.4	Summary of Hematology Shift from Baseline
14.3.4.9	Summary of Vital Signs
14.3.4.10.1	Summary of Electrocardiogram Parameters
14.3.4.10.2	Summary of Electrocardiogram Categorical Results

15.2 LIST OF LISTINGS

Listing Number	Listing Title
16.2.1.1	Subject Dispositions
16.2.1.2	Subject Accountability
16.2.2	Protocol Deviations
16.2.3.1	Subject Randomization
16.2.3.2	Analysis Population Information
16.2.3.3	Entry Criteria
16.2.4.1	Demographics
16.2.4.2	PH-ILD History
16.2.4.3	Medical History
16.2.4.4	Concomitant Medications
16.2.5	Study Drug Dosing
16.2.6.1	6-Minute Walk Test
16.2.6.2	6MWT Information with Imputed Data – Peak 6MWD
16.2.6.3	6MWT Information with Imputed Data – Trough 6MWD
16.2.6.4	Plasma NT-proBNP (pg/mL)

Listing Number	Listing Title
16.2.6.5	Clinical Worsening Events
16.2.6.6	The St. George's Hospital Respiratory Questionnaire
16.2.6.7	The St. George's Hospital Respiratory Questionnaire Score by Domain
16.2.6.8	Hospitalizations
16.2.6.9	Death Records
16.2.6.10	RHC and Hemodynamic Measures
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Adverse Events Leading to Discontinuation of Study Drug
16.2.7.4	Exacerbations of Underlying Lung Disease
16.2.8.1	Pulse Oximetry and DSP
16.2.8.2	Supplemental Oxygen
16.2.8.3	Pulmonary Function Test Results
16.2.8.4	Laboratory Results – Clinical Chemistry
16.2.8.5	Laboratory Results – Hematology
16.2.8.6	Pregnancy Status
16.2.8.7	Vital Signs
16.2.8.8	ECG Results

15.3 LIST OF FIGURES

Figure Number	Figure Title
14.2.1	Mean Change from Baseline in Peak 6MWD (meter) by Visit
14.2.2	Mean Change from Baseline in Peak 6MWD (meter) at Week 16 by Inhaled Treprostinil Dose at Week 16
14.2.3	Forest Plot on Subgroup Analyses of Peak 6MWD (meter) at Week 16
14.2.4	Kaplan-Meier Plot of Time to Clinical Worsening Events