3Document Type:	Statistical Analysis Plan	**Protocol / Study No.:**	TIP-PH-101
Finalization Date:	24-JUN-2020	**Total Number of Pages including Appendices:**	24
Classification:	Confidential		

Title:

An Open-label, Clinical Study to Evaluate the Safety and Tolerability of Treprostinil Inhalation Powder (TreT) in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso

Author: [redacted]

TABLE OF CONTENTS

Table of In-Text Tables

Table of In-Text Figures

ABBREVIATIONS AND DEFINITIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
FC	Functional Class
HR	Heart rate
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact
PDE5-I	Phosphodiesterase type 5 inhibitor
PK	Pharmacokinetic(s)
PQ-ITD	Preference Questionnaire for Inhaled Treprostinil Devices
PT	Preferred term
QID	Four times daily
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sGC	Soluble guanylate cyclase
SOC	System organ class
TreT	Treprostinil Inhalation Powder
WHO	World Health Organization

1 PREFACE

This plan provides further details of the planned analyses for the TIP-PH-101 study as presented in the study protocol. 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.

1.1 CHANGES TO STATISTICAL ANALYSIS PLAN

The following changes have been made to the SAP:

- Addition of accommodations for COVID-19 pandemic including additional summary tables
- Minor changes to visit timing due to protocol amendment
- Adjustments to visit windows due to protocol amendment
- Removal of Optional Extension Phase summaries for demographics and baseline characteristics, medical history, pulmonary arterial hypertension (PAH) history, and concomitant medications
- Modification of background therapy listing and summary
- Removal of oxygen assessments from 6-minute walk listing since these data were not collected

1.2 COVID-19 ACCOMMODATIONS

The COVID-19 pandemic is expected to have various effects on clinical trials. Due to closure of sites during the COVID-19 pandemic, it is expected that there will be more missing data than usual, more protocol deviations may be observed, changes in patient population may occur, adverse events and concomitant medications may be underreported, and/or treatment interruption may occur. Twenty subjects were enrolled prior to enrollment hold/closures at sites due to the pandemic. These subjects will comprise the pre-pandemic subjects. All other subjects enrolled later will comprise the post-pandemic subjects.

1.2.1 Missing Data

It is known that 3 subjects were unable to provide pharmacokinetic (PK) assessments at the Treatment Phase Week 3 Visit. All other subjects had completed the Treatment Phase Week 3 Visit prior to site closures, and no new subjects were enrolled during the time of site closures. Subjects were unable to attend visits during the Optional Extension Phase. Visit windows will be expanded to allow for out-of-window visits to be slotted to a scheduled visit.

1.2.2 Protocol Deviations

Protocol deviations are reviewed periodically, at data cutoff, and at the end of the study. No per-protocol analyses were planned for this study, so no modifications to the analyses due to protocol deviations will be done.

1.2.3 Patient Population Characteristics

In order to assess whether changes in the population characteristics have occurred, separate demographics and baseline characteristic summaries will be created based on enrollment pre- or post-pandemic.

1.2.4 Impact on Safety Evaluation

In order to assess whether adverse events (AEs) were underreported during site closures, the rate of AEs will be calculated pre- and post-pandemic for those subjects who remained in the study during site closures. No assessment of underreporting of concomitant medications is planned.

1.2.5 Impact on PK Evaluation

Only 3 subjects were unable to provide PK assessments at the Treatment Phase Week 3 Visit due to the pandemic. This will result in a smaller PK population, but there are no planned changes to the analyses.

1.2.6 Treatment Interruptions

Since the extension phase is optional, no modifications will be made for treatment interruptions. The assumption that subjects were on treatment throughout is conservative.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective of this clinical study is to evaluate the safety and tolerability of Treprostinil Inhalation Powder (TreT) in subjects with PAH currently treated with Tyvaso®.

2.1.2 Secondary Objectives

A secondary objective of this clinical study is to evaluate systemic exposure and PK of treprostinil in subjects with PAH when delivered as Tyvaso and TreT. Additionally, this study will evaluate 6-Minute Walk Distance (6MWD) at study entry and after 3 weeks of treatment with TreT. The Optional Extension Phase of this study will evaluate long-term safety and tolerability of TreT in subjects with PAH previously treated with Tyvaso. Further, this study will evaluate subject satisfaction with and preference for inhaled treprostinil devices with the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD) and patient-reported PAH symptoms and impact with the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) Questionnaire.

2.2 ENDPOINTS

The following endpoints will be analyzed:

- PK assessments
- AEs
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical laboratory assessments
- 6MWD
- PQ-ITD
- PAH-SYMPACT Questionnaire domain scores

3 STUDY DESIGN

This is a Phase 1b safety and tolerability single-sequence study in which subjects on a stable regimen of Tyvaso will switch to a corresponding dose of TreT. At Baseline, subjects currently taking stable doses of Tyvaso (6 to 12 breaths 4 times daily [QID]) will take a dose of Tyvaso in the clinic and undergo PK assessments, safety assessments, and a 6-Minute Walk Test (6MWT). Following the in-clinic assessments, subjects will switch from Tyvaso to the corresponding dose of TreT and take their first dose of TreT in the clinic. Following 3 weeks of treatment with TreT, subjects will return to the clinic and receive 1 dose of TreT and undergo PK assessments, safety assessments, and a 6MWT as performed at the Baseline Visit.

Following the Week 3 Visit, subjects will be offered the opportunity to participate in the Optional Extension Phase of the study. Subjects who elect to discontinue TreT at the end of the Treatment Phase will return to the clinic in 2 weeks for an End of Study Visit. Subjects who elect to enter the Optional Extension Phase will remain on TreT and attend study visits every 8 weeks until the study is terminated or the drug/device becomes commercially available. If the subject discontinues TreT prematurely during the Optional Extension Phase, he/she must return to the clinic as soon as possible for an Early Termination Visit.

Screening Phase: Prospective subjects will be assessed during the Screening Phase to determine eligibility for the study. The Screening Visit must occur within 14 days prior to Baseline. During this Screening Phase, eligible subjects will sign the Informed Consent Form and undergo screening assessments. Subjects who satisfy all eligibility criteria during the Screening Phase may return to the clinic at Baseline for enrollment. If subjects are able to satisfy all eligibility criteria on the same day, a combined Screening/Baseline Visit may be conducted.

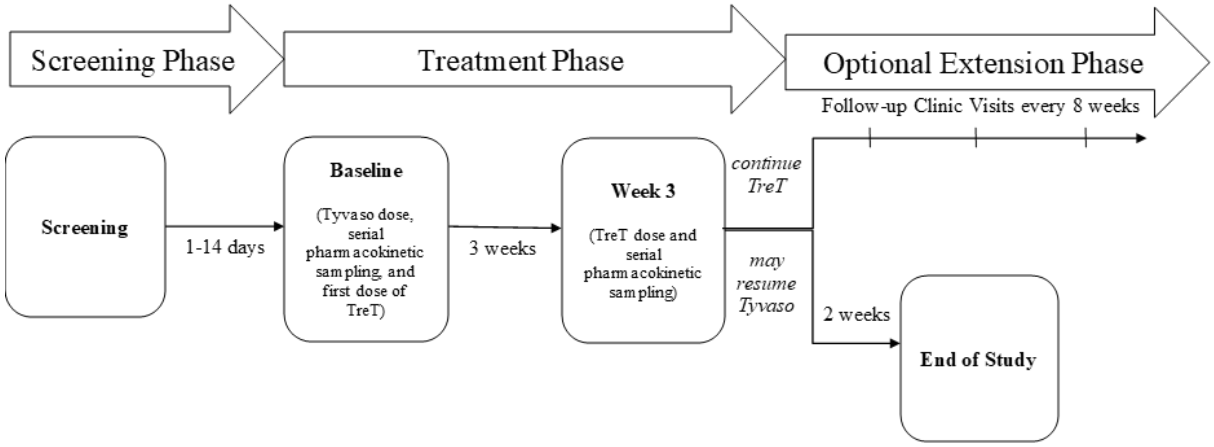
Treatment Phase: The Treatment Phase consists of 2 study visits to the clinic separated by 3 weeks of treatment with TreT. At Baseline, subjects will receive 1 dose of Tyvaso in the clinic and undergo PK assessments (at the following timepoints: 15 minutes before dose and 5, 10, 15, 30, 45, 90, 120, 180, 240, and 300 minutes after dose), safety assessments, and a 6MWT. No additional dose of Tyvaso will be administered, nor will TreT be started, until after the PK sampling assessment is complete. Following these assessments, subjects will be assigned a corresponding dose of TreT based upon their current stable Tyvaso dose and will receive the first dose of TreT in the clinic. Each subject will receive TreT QID by oral inhalation for 3 weeks. Following 3 weeks of treatment, subjects will return to the clinic and receive 1 dose of TreT in the clinic and undergo PK assessments, safety assessments, and a 6MWT as performed at the Baseline Visit. Questionnaires evaluating patient preference for inhaled treprostinil devices and patient-reported PAH symptoms and impact will also be administered. At each study visit, AEs will be assessed, vital signs will be recorded, and a physical examination, including oropharyngeal examination, will be performed. Following the Week 3 Visit, subjects may choose to participate in the Optional Extension Phase of the

study. If the subject does not elect to participate in the Optional Extension Phase of the study, he/she must discontinue TreT, may resume Tyvaso therapy, and must return to the clinic 2 weeks after TreT discontinuation for an End of Study Visit. Blood samples for an optional evaluation of change in biomarkers (specific targets to be determined) will be collected at the Baseline Visit and Week 3 Visit. An additional blood sample for an optional evaluation of whole genome sequence will be collected at the Baseline Visit.

Optional Extension Phase: The Optional Extension Phase will occur following completion of the Treatment Phase and continue with clinic visits every 8 weeks until the study is terminated for any reason or the drug/device becomes commercially available. To be eligible for the Optional Extension Phase, subjects must complete the Treatment Phase, elect to continue TreT, and agree to attend follow-up visits in the clinic. Dosing titration will be encouraged during the Optional Extension Phase; the dose of TreT should be titrated upward, as clinically tolerated, to identify a maximum stable dose in each subject. Subjects who discontinue TreT must complete an Early Termination Visit as soon as possible. A blood sample for an optional evaluation of change in biomarkers will be collected at the Week 51 Visit.

A study flow chart is available in Figure 3-1.

Figure 3-1 Study Flow Chart



4 RANDOMIZATION

Subjects are not randomized. Subjects will be assigned treatment with TreT based on their current Tyvaso regimen as detailed in Table 4-1. An Interactive Response Technology (IRT)

will be utilized to assign each subject the appropriate study drug for the 3-week Treatment Phase and the Optional Extension Phase.

Table 4-1 Treatment Assignments

Study Entry	Treatment Phase	
Tyvaso Dose (QID)	**TreT Dose (QID)**	**Device Requirement**
6 to 7 breaths	32 mcg	32 mcg cartridge
8 to 10 breaths	48 mcg	48 mcg cartridge
11 to 12 breaths	64 mcg	32 mcg + 32 mcg cartridges

Abbreviations: QID, four times daily; TreT, Treprostinil Inhalation Power.

5 STRATIFICATION

No stratification will be done in this study.

6 SEQUENCE OF PLANNED ANALYSES

After all subjects complete the Treatment Phase, the Treatment Phase database will be locked and analysis of the data from the Treatment Phase will be carried out. Any available data from the Optional Extension Phase will also be analyzed at this time. At the completion of the study, final analyses of the Optional Extension Phase data will be conducted.

7 SAMPLE SIZE CONSIDERATIONS

For this study, the total sample size is estimated to be 45 subjects and is not based on power calculations.

8 ANALYSIS POPULATIONS

The Safety Population is defined as all subjects who received at least 1 dose of TreT during the Treatment Phase. All analyses will be performed on this Safety Population unless otherwise specified.

9 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 TreT dose, 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 included in the Safety Population will be flagged.

In general, the data will be summarized by scheduled assessment within each TreT dose and overall and separately for each phase. 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. Whenever practical, categories of discrete variables will be ordered and labelled as they appear in the eCRF, and all categories represented on the eCRF will be included in summaries, even when they do not apply to any subjects in the study.

All statistical calculations will be completed using SAS® Version 9.4 or above.

9.1 COVARIATES

There are no planned covariates.

9.2 EXAMINATION OF SUBGROUPS

The following subgroup analyses will be performed if the data warrant:

- Background therapy (None, monotherapy, or 2 or more background medications)
- Background therapy (endothelin receptor antagonist [ERA], phosphodiesterase type 5 inhibitor [PDE5-I], soluble guanylate cyclase [sGC] stimulator)
- World Health Organization (WHO) Functional Class (FC) (Class I, Class II, or Class III)
- Baseline 6MWD (<350 meters or ≥350 meters).

9.3 PREMATURE DISCONTINUATION AND MISSING DATA

Subjects may not complete the Treatment Phase or the Optional Extension Phase for the following reasons: death, disease progression, adverse event, lost to follow-up, protocol violation, withdrawal of consent, or termination of the study by the Sponsor. All available data from all subjects in the Safety Population will be used as detailed in this analysis plan.

9.4 MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustments for multiplicity will be done.

9.5 DERIVED AND TRANSFORMED DATA

9.5.1 Baseline

In general, Baseline for any assessment will be defined as the measurement obtained at the Baseline Visit. If the assessment is not collected at the Baseline Visit, the last measurement prior to the first TreT dose will be defined as Baseline.

9.5.2 QT Intervals

Adjustments to the QT intervals will be calculated as shown in Table 9-1.

Table 9-1 Adjustments to QT Intervals

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

Abbreviations: HR, heart rate; QTc, QT interval corrected for heart rate.

9.6 ASSESSMENT WINDOWS

For any data summarized by scheduled visit, an analysis visit window will be used. In the protocol, the visit window for the Week 3 Visit and the End of Study Visit is ±3 days. The visit window for the Optional Extension Phase Visits is ±5 days. In order to allow slotting of discontinuation visits and visits outside the planned schedule, the visit windows have been expanded for analysis purposes. The scheduled visits, as recorded on the eCRFs, and the corresponding target days and study day intervals are specified in Table 9-2. The analysis visit will be derived based on the information specified in Table 9-2.

Table 9-2 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
ECGs		
Baseline	1	Study Day ≤1 (prior to the date of the first dose)
End of Study Visit		Last assessment after Study Day 1
PQ-ITD		
Baseline	1	Study Day ≤1 (prior to the date of the first dose)
Week 3	22	1< Study Day ≤ Last assessment day during Treatment Phase
End of Study Visit		Last assessment after Study Day 1
PAH-SYMPACT		
Baseline	1	Study Day ≤1 (prior to date of the first dose)
Week 3	22	1< Study Day ≤ Last assessment day during Treatment Phase
Week 11	78	Any assessment during Optional Extension Phase
End of Study Visit		Last assessment after Study Day 1
Clinical laboratory assessments, vital signs, 6MWT		
Baseline	1	Study Day ≤1 (prior to date of the first dose)
Week 3	22	1< Study Day ≤ Last assessment day during Treatment Phase
Week 11	78	Last assessment day during Treatment Phase < Study Day ≤106
Subsequent weeks (every 8 weeks after Week 11)	Week*7+1	Target Study Day-28 < Study Day ≤ Target Study Day+28 or last assessment day during the Optional Extension Phase for final visit
End of Study Visit		Last assessment in the study

Abbreviations: 6MWT, 6-Minute Walk Test; ECG, electrocardiogram; PAH-SYMPACT, Pulmonary Arterial Hypertension-Symptoms and Impact; PQ-ITD, Preference Questionnaire for Inhaled Treprostinil Devices; *, times.
Note: Study Day = (Assessment Date) − (First Dosing Date) +1

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.

10 STUDY POPULATION

Unless otherwise specified, all analyses will be performed on the Safety Population as defined in Section 8.

10.1 PATIENT ACCOUNTABILITY

All subjects' disposition information will be listed by individual subject number, including premature study discontinuation status during the Treatment Phase and the Optional Extension Phase, primary reason for premature study discontinuation, number of days on TreT, and enrollment in the Optional Extension Phase.

The listing of subject accountability will include the dates of informed consent, the date of first TreT dose and the date of last TreT dose, and Tyvaso dose at entry. The number of subjects who received TreT, who completed the Treatment Phase, who completed the Optional Extension Phase, and reasons for study discontinuation will be summarized by TreT dose and overall.

10.2 ELIGIBILITY CRITERIA

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. The total number of entry criteria violations and the number of violations for each criterion will be summarized by TreT dose and overall.

Additional protocol deviations may 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, pharmacokinetic, 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 number of protocol deviations and the number of protocol deviations by type will also be summarized.

10.3 OTHER DESCRIPTIONS OF STUDY POPULATION

10.3.1 Demographics

All demographic data will be listed for all subjects, including assessment date, date of birth, age, sex, ethnicity, race, weight, height, and body mass index (BMI). Age, age category (<65 years of age and ≥65 years of age), sex, ethnicity, race, height, weight, and BMI will be summarized by TreT dose and overall. To assess possible changes in the patient population, an additional summary will be created for demographics by time of enrollment: pre- or post-pandemic.

10.3.2 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, and whether the condition is ongoing at study entry. These medical conditions will be summarized by PT within each SOC by TreT dose and overall.

The listing of PAH history will include date of PAH diagnosis, time since PAH diagnosis, current PAH diagnosis, and WHO FC. The current PAH diagnosis, time since PAH diagnosis, and WHO FC will be summarized by TreT dose and overall. To assess possible changes in the patient population, an additional summary will be created for PAH history by time of enrollment: pre- or post-pandemic.

10.3.3 Concomitant and Background Medications

All concomitant medications recorded on the eCRF will be mapped to a standard name and Anatomical Therapeutic Chemical (ATC) Levels 1 to 4 using the WHODrug Global. The ATC Levels 2 and 4 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). A summary of concomitant medications present at Baseline, a summary of concomitant medications added during the Treatment Phase, and a summary of concomitant medications added during the Optional Extension Phase will include the frequency and percentage of subjects in each TreT dose group and overall. If ATC Level

4 is not available for a medication, ATC Level 3 will be substituted. If ATC Level 3 is not available, ATC Level 2 will be substituted. If ATC Level 2 is not available, ATC Level 1 will be substituted.

The listing of PAH background medications will include the generic term, date initiated, current total daily dose, and date current dose initiated. The number of subjects receiving each PAH background medication and the current total daily dose will be summarized by TreT dose and overall. A similar listing and summary table will also be created for Tyvaso. Additionally, the number and percentage of subjects receiving ERA only, PDE5-I only, and ERA + PDE5-I will be calculated by TreT dose and overall.

11 EFFICACY ANALYSES

11.1 6-MINUTE WALK TEST

All 6MWT data will be listed for all subjects. For each scheduled assessment, this listing will include the date the test was performed (or date the test was intended to be performed if subject is unable to attempt the test), start time of the test, nominal time point, last TreT or Tyvaso dose, hours from last TreT or Tyvaso dose to 6MWT start, if walk was attempted, total distance walked (in meters), and any circumstances that adversely affected the walk (if any) including reason for not attempting test (if any).

Summaries of 6MWT and corresponding changes from Baseline will be provided by TreT dose and overall at each visit during the Treatment Phase and Optional Extension Phase. Change in 6MWD will be assessed by a paired t-test at each week for the overall group. Additionally, a line graph presenting the change from Baseline at each week of the Treatment Phase and Optional Extension Phase will be produced.

11.2 PREFERENCE QUESTIONNAIRE FOR INHALED TREPROSTINIL DEVICES

Responses to the PQ-ITD will be listed for all subjects. The listing will include the date of the questionnaire, nominal study visit, and all responses for each subject.

Summaries for each question in the PQ-ITD will be provided by TreT dose and overall at Baseline, Week 3, and End of Study Visit. Additionally, figures presenting overall

satisfaction with the inhaler at Baseline, Week 3, and End of Study visit will be produced. For each question that is assessed at both the Baseline and Week 3 visits, the Mantel-Haenszel mean score statistic will be computed to determine if the distribution of assessments for each device is the same. The pseudo SAS code for this analysis is as follows:

```
proc freq;
  tables usubjid*avisit*assessment / cmh;
run;
```

where usubjid is the subject identifier, avisit is the visit identifier (Baseline and Week 3), assessment is the response (Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree), and cmh specifies the Cochran-Mantel-Haenszel statistics.

11.3 PAH-SYMPACT

Responses to the PAH-SYMPACT Questionnaire will be listed for all subjects. The listing will include the date of the questionnaire, nominal study visit, all responses for each subject, and the computed domain scores.

Summaries for each question in the PAH-SYMPACT will be provided by TreT dose and overall at Baseline, Week 3, Week 11 of the Optional Extension Phase, and End of Study Visit. Additionally, summaries of each domain score (Cardiopulmonary Symptoms, Cardiovascular Symptoms, Physical Impacts, Cognitive/Emotional Impacts) will be calculated by TreT dose and overall at Baseline, Week 3, Week 11 of the Optional Extension Phase, and End of Study Visit. Changes in domain scores will be assessed by paired t-tests at Week 3.

12 SAFETY ANALYSES

All safety analyses will be performed on the Safety Population (see Section 8).

12.1 EXTENT OF EXPOSURE

All study drug dosing will be listed for all subjects. The listing will include TreT dose (in mcg), date of first dose, and date of last dose. The duration of exposure and TreT dose during the Treatment Phase and during the Optional Extension Phase will be summarized by assigned TreT dose and overall.

For study treatment compliance, the number and percentage of days with at least 1 dose of TreT will be calculated and summarized by TreT dose and overall for both the Treatment Phase and Optional Extension Phase. Additionally, for each subject, compliance will be calculated as (Total number of doses taken divided by total number of doses supposed to be taken) times 100% and summarized by TreT dose and overall for both the Treatment Phase and Optional Extension Phase.

12.2 ADVERSE EVENTS

All AEs will be coded to the appropriate PT and SOC using MedDRA. AEs will be listed by TreT dose including all details recorded on the eCRF plus an indicator of whether the event was treatment emergent. Treatment-emergent AEs are those AEs with an onset date equal to or after the start date of TreT. 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 and will be prepared for the Treatment Phase and the combined Treatment Phase and Optional Extension Phase. The non–treatment-emergent AEs (the AEs occur after signing the Informed Consent Form but before receiving TreT) will be listed but not included in summary tables.

All summaries will include the number and percentage of subjects experiencing each type of AE and the total number of each type of AE, in order of overall frequency and/or SOC. Serious adverse events (SAEs) 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 TreT dose.

AEs 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 the listing

of deaths, information for all subjects who die during the study period from Baseline to the end of the study (including 30 days after the last TreT dose) will be included.

To assess possible underreporting of AEs, an additional summary will be created for AEs by time of enrollment: pre- or post-pandemic.

12.3 CLINICAL LABORATORY ASSESSMENTS

12.3.1 Clinical Chemistry and Hematology

Blood for the measurement and evaluation of clinical chemistry and hematology collected at study visits will be used to assess treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Values will be obtained for the parameters listed in Table 12-1.

Table 12-1 Clinical Laboratory Parameters

Electrolyte Panel	Chemistry Panel	Hematology Panel
Bicarbonate	Alanine aminotransferase	Hemoglobin
Chloride	Aspartate aminotransferase	Hematocrit
Potassium	Bilirubin (total and indirect)	Red blood cell count
Sodium	Creatinine	White blood cell count
	Blood urea nitrogen	Platelet count

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 TreT dose and overall.

For each parameter, the frequency and percentage of subjects within each TreT dose and overall 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.

12.3.2 Pregnancy Testing

Women of childbearing potential will undergo a urine pregnancy test at study visits. A listing of pregnancy test results will be provided.

12.4 VITAL SIGNS

All vital sign assessments will be listed for all subjects. This listing will include weight, BMI, heart rate (HR), systolic and diastolic blood pressures, and respiratory rate. The vital sign results at each assessment and changes for each post-Baseline assessment will be descriptively summarized by TreT dose and overall at each visit during the Treatment Phase and Optional Extension Phase.

12.5 ELECTROCARDIOGRAMS

All ECG assessments will be listed for all subjects. This listing will include the HR, the ECG interval from the beginning of the QRS complex to the end of the T wave (QT interval), the QT interval corrected for HR (QTc) (calculated using formulas by both Bazett and Fridericia as described in Section 9.5.2), the time between the P wave and the beginning of the QRS complex in ECG (PR interval), the electrocardiographic wave (QRS) duration, ECG results (normal/abnormal), whether there were clinically significant changes from the Screening Visit, whether abnormalities were present, and details and comments on any abnormalities. The ECG results at Baseline and changes for each post-Baseline assessment will be descriptively summarized by TreT dose and overall at each visit during the Treatment Phase and Optional Extension Phase. 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 the number and percentage of subjects reporting at each visit by TreT dose and overall at each visit during the Treatment Phase and Optional Extension Phase.

13 PHARMACOKINETICS

A listing will include the date and time of specimen collection for pharmacokinetics. Details of the analyses of the PK data will be provided in a separate SAP.

14 BIOMARKERS AND WHOLE GENOME SEQUENCING

A listing will include the date and time of specimen collection for biomarkers and whole genome sequencing. Details of the analyses of the optional biomarkers and optional whole genome sequencing will be provided in a separate SAP.

15 APPENDICES

15.1 LIST OF TABLES

Table Number	Table Title
14.1.1	Summary of Subject Accountability
14.1.2	Summary of TreT Exposure
14.1.3.1	Summary of Entry Criteria Violations
14.1.3.2	Summary of Protocol Deviations
14.1.4	Summary of Demographics
14.1.4.1	Summary of Demographics by Time of Enrollment
14.1.5	Summary of Medical History
14.1.6	Summary of PAH History
14.1.6.1	Summary of PAH History by Time of Enrollment
14.1.7.1	Summary of Concomitant Medications Ongoing at Baseline
14.1.7.2	Summary of Concomitant Medications Added during the Treatment Phase
14.1.7.3	Summary of Concomitant Medications Added during the Optional Extension Phase
14.1.7.4	Summary of Background PAH Medications
14.1.7.5	Summary of Tyvaso Medication History
14.1.8	Summary of TreT Dosing
14.1.9	Summary of TreT Treatment Compliance
14.2.1.1	Summary and Analysis of 6MWD (meter) during Treatment Phase
14.2.1.2	Summary of 6MWD (meter) during Optional Extension Phase
14.2.2.1	Summary of Preference Questionnaire for Inhaled Treprostinil Devices
14.2.2.2	Analysis of Preference Questionnaire for Inhaled Treprostinil Devices
14.2.3	Summary and Analysis of PAH-SYMPACT Questionnaire
14.3.1.1	Overall Summary of Adverse Events
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
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	Listing of Deaths
14.3.1.11	Listing of Serious Adverse Events

Table Number	Table Title
14.3.1.12	Summary of Adverse Events by System Organ Class, Preferred Term, and Time of Enrollment
14.3.2.1	Summary of Clinical Chemistry
14.3.2.2	Summary of Clinical Chemistry Shift from Baseline
14.3.2.3	Summary of Hematology
14.3.2.4	Summary of Hematology Shift from Baseline
14.3.3.1	Summary of Vital Signs
14.3.3.2	Summary of Electrocardiogram Parameters
14.3.3.3	Summary of Electrocardiogram Categorical Results

15.2 LIST OF LISTINGS

Listing Number	Listing Title
16.2.1.1	Subject Disposition
16.2.1.2	Subject Accountability
16.2.2.1	Entry Criteria
16.2.2.2	Protocol Deviations
16.2.4.1	Demographics
16.2.4.2	PAH History
16.2.4.3	Medical History
16.2.4.4	PAH Background Medications
16.2.4.5	Tyvaso Medication History
16.2.4.6	Concomitant Medications
16.2.5	TreT Dosing
16.2.6.1	6-Minute Walk Test
16.2.6.2	Preference Questionnaire – Inhaled Treprostinil Device (Part 1 of 2)
16.2.6.2	Preference Questionnaire – Inhaled Treprostinil Device (Part 2 of 2)
16.2.6.3.1	PAH-SYMPACT Questionnaire (Cardiopulmonary Symptoms)
16.2.6.3.2	PAH-SYMPACT Questionnaire (Cardiovascular Symptoms)
16.2.6.3.3	PAH-SYMPACT Questionnaire (Physical Impacts)
16.2.6.3.4	PAH-SYMPACT Questionnaire (Cognitive/Emotional Impacts)
16.2.7.1	Adverse Events
16.2.7.2	Adverse Events Leading to Discontinuation of TreT
16.2.8.1	Clinical Chemistry
16.2.8.2	Hematology
16.2.8.3	Pregnancy Test Results
16.2.8.4	Other Laboratory Tests
16.2.8.5	Vital Signs
16.2.8.6	ECG Results

15.3 LIST OF FIGURES

Figure Number	Figure Title
14.2.1	Summary of PQ-ITD at Week 3 of Treatment Phase - Response to: Overall, I am satisfied with the inhaler
14.2.2	Summary of PQ-ITD at End of Study - Response to: Overall, I am satisfied with the inhaler
14.2.3	Mean Change from Baseline in 6MWD (meters) by Visit