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

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Protocol Date: 30 January 2019
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Amendment 2: 02 April 2020

LIST OF CONTACTS FOR STUDY

Study Sponsor:	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709
SAE Reporting:	UT Global Drug Safety [redacted]
Clinical Laboratory:	Covance Laboratories Inc. [redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "An Open-label, Clinical Study to Evaluate the Safety and Tolerability of Treprostinil Inhalation Powder in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso," Protocol Amendment 2 dated 02 April 2020 and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56 and 312 and any local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of United Therapeutics Corp.

I also have read the current Clinical Investigator's Brochure for Treprostinil Inhalation Powder and acknowledge that review of the information contained in the Clinical Investigator's Brochure is a requirement for Investigators before using Treprostinil Inhalation Powder in a clinical study.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and Ethics Committee/Institutional Review Board approval documents have been obtained.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

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
Study Phase	1b
Indication	Pulmonary arterial hypertension (WHO Group 1)
Primary Objective	To evaluate the safety and tolerability of Treprostinil Inhalation Powder (TreT) in subjects with pulmonary arterial hypertension (PAH) currently treated with Tyvaso®
Secondary Objective(s)	1. To evaluate systemic exposure and pharmacokinetics (PK) of treprostinil in subjects with PAH when delivered as Tyvaso and TreT 2. To evaluate 6-Minute Walk Distance (6MWD) at study entry and after 3 weeks of treatment with TreT 3. To evaluate long-term safety and tolerability of TreT in subjects with PAH previously treated with Tyvaso 4. To evaluate subject satisfaction with and preference for inhaled treprostinil devices with the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD). 5. To evaluate patient-reported PAH symptoms and impact with the PAH-Symptoms and Impact (PAH-SYMPACT) Questionnaire.
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 in clinic 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 follow-up study visits that will occur 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 clinic as soon as possible for an Early Termination Visit.
Sample Size	For this study, total sample size is estimated to be 45 subjects and is not based on power calculations.
Summary of Subject Eligibility Criteria	Inclusion Criteria: 1. Subject voluntarily gives informed consent to participate in the study. 2. Subject is aged 18 years or older at the time of signing informed consent. 3. Women of childbearing potential must be nonpregnant and nonlactating, and will: a. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or b. Use 2 medically acceptable, highly effective forms of contraception for the duration of study, and at least 30 days after discontinuing TreT. Medically acceptable, highly effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), intrauterine devices or systems, and barrier methods (such as a condom or diaphragm) when used with a spermicide. 4. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing TreT. 5. Subject is diagnosed with PAH as defined by the following World Health Organization (WHO) Group 1 categories: a. Idiopathic/familial b. Associated with unrepaired or repaired congenital systemic-to-pulmonary shunts (repaired ≥5 years prior to screening) c. Associated with collagen vascular disease d. Associated with human immunodeficiency virus e. Associated with appetite suppressant/other drug or toxin use 6. Subject must have started Tyvaso ≥3 months prior to the Baseline Visit and must currently be on a stable regimen (no change in dose within 30 days of Baseline Visit) of Tyvaso (6 to 12 breaths QID). 7. Baseline 6MWD ≥150 m.

8. If currently receiving other approved background therapy for PAH (eg, endothelin receptor antagonist or phosphodiesterase-5-inhibitor or both), the subject must be on a stable dose with no additions or discontinuations for a minimum of 30 days prior to Screening.
9. The subject has had evidence of forced expiratory volume in 1 second (FEV_1) ≥60% and FEV_1/forced vital capacity ratio ≥60% during the 6 months prior to enrollment.
10. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing, and likely to be cooperative with protocol requirements, including all study visits.

Exclusion Criteria:

1. Subject is pregnant or lactating.
2. Subject has been diagnosed with pulmonary hypertension for reasons other than WHO Group 1 as outlined in Inclusion Criterion 5 (including but not limited to portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, hemolytic anemia, sarcoidosis).
3. Subject has a history of uncontrolled sleep apnea, parenchymal lung disease, or hemodynamically significant left-sided heart disease (including but not limited to aortic or mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, or coronary artery disease).
4. Subject is currently taking any other prostacyclin analogue or agonist, including but not limited to, selexipag, epoprostenol, iloprost, or beraprost; except for acute vasoreactivity testing.
5. Subject experienced an acute exacerbation of disease or hospitalization for any reason within 30 days of Screening Visit or between Screening and Baseline.
6. Subject is WHO Functional Class IV at Screening.
7. Subject has used any investigational drug/device or participated in any other investigational study with therapeutic intent within 30 days prior to Screening Visit.
8. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant idiosyncratic reaction to treprostinil or excipients in the investigational product.

	9. Subject has conditions that, in the opinion of the Investigator, would make the subject ineligible. 10. Subject is not able to perform inhalation maneuvers that meet inspiratory training criteria. 11. Subject has a musculoskeletal disorder (eg, arthritis affecting the lower limbs, recent hip or knee joint replacement) or any disease that would likely be the primary limit to ambulation, or is connected to a machine that is not portable enough to allow for a 6MWT. 12. Subject has had a new type of chronic therapy (including but not limited to oxygen, a different class of vasodilator, diuretic, and digoxin) for pulmonary hypertension added within 30 days of the Screening Phase. 13. Initiation of pulmonary rehabilitation within 12 weeks prior to the Baseline Visit.
Drug Dosage and Formulation	The treatments are assigned based on current stable Tyvaso dose. Each subject will receive a corresponding dose of TreT for 3 weeks during the Treatment Phase.

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

Control Group	None
Route of Administration	TreT will be administered via a dry powder inhaler in 3 dose levels supplied as cartridges filled to provide 32 µg, 48 µg, and 64 µg of treprostinil. Tyvaso inhalation solution will be administered via ultrasonic nebulization using the commercially available Tyvaso Inhalation System.
Procedures	**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 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 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 during the Treatment Phase, adverse events (AEs) will be assessed, vital signs will be recorded, and a physical 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, and must return to the clinic 2 weeks after TreT discontinuation for an End of Study 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.
Statistical Considerations	Plasma concentrations of treprostinil above the lower limit of quantitation will be used to calculate area under the curve from time 0 to 300 minutes ($AUC_{0\text{-}300}$) and maximal drug concentration (C_{max}) for each treatment. PK and safety parameters will be summarized using descriptive statistics. The 6MWT results will also be summarized using descriptive statistics. The number and percent of subjects with AEs will be tabulated for treatment phases by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term by relationship to treatment and severity.

Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709 USA

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LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
AUC	Area under the curve
C_{max}	Maximal drug concentration
DBP	Diastolic blood pressure
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERA	Endothelin receptor antagonist
FEV_1	Forced expiratory volume in 1 second
FDA	Food and Drug Administration
FDKP	Fumaryl diketopiperazine
GCP	Good Clinical Practice
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact
PDE5-I	Phosphodiesterase type 5 inhibitor
PE	Physical examination
PFT	Pulmonary function test
PGI_2	Prostacyclin
PK	Pharmacokinetic(s)
PQ-ITD	Preference Questionnaire for Inhaled Treprostinil Devices
PRO	Patient reported outcome
QID	4 times daily
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
sGC	Soluble guanylate cyclase

TreT	Treprostinil Inhalation Powder
UTC	United Therapeutics Corporation
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary arterial hypertension (PAH), defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance, is a severe hemodynamic abnormality associated with a variety of diseases and syndromes. Elevation in pulmonary arterial pressure causes an increase in right ventricular afterload, impairing right ventricular function, and ultimately leading to heart failure and death (Rubin 1997).

There are 3 major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. There are several metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators, nitric oxide and prostacyclin (PGI_2), and the vasoconstrictor, endothelin-1. These substances affect both vascular tone and remodeling, leading to their use as pharmacologic targets (Farber 2004).

Approved pharmacotherapies for PAH in the US include intravenous (IV) PGI_2 (epoprostenol sodium or Flolan, Veletri®); the PGI_2 analogues, subcutaneous, IV, and inhaled treprostinil (Remodulin®, Tyvaso®), oral treprostinil diethanolamine (also referred to as treprostinil diolamine; Orenitram®), oral selexipag (Uptravi®), and inhaled iloprost (Ventavis®); the phosphodiesterase type 5 inhibitors (PDE5-Is), tadalafil (Adcirca®) and sildenafil (Revatio®); the oral endothelin receptor antagonists (ERAs), bosentan (Tracleer®), ambrisentan (Letairis®, Volibris®), and macitentan (Opsumit®); and a soluble guanylate cyclase (sGC) stimulator, riociguat (Adempas®).

1.2 INHALED TREPROSTINIL BACKGROUND

1.2.1 Treprostinil Inhalation Powder

United Therapeutics Corporation (UTC) is developing a combination drug-device product which is comprised of a dry powder formulation of Treprostinil Inhalation Powder (TreT) and a small, portable, dry powder inhaler. The dry powder contains treprostinil and an inhalation excipient, fumaryl diketopiperazine (FDKP), which is an excipient present in Afrezza®, an Food and Drug Administration (FDA)-approved drug product that is listed in the FDA Inactive Ingredient Database.

1.2.1.1 Active Pharmaceutical Ingredient: Treprostinil

Treprostinil, [[(1R,2R,3aS,9aS) 2,3,3a,4,9,9a hexahydro 2 hydroxy 1 [(3S) 3 hydroxyoctyl] 1H benz [f]inden 5 yl]oxy]acetic acid, is a chemically stable tricyclic analogue of PGI_2. The pharmacology of treprostinil has been extensively characterized in well-established models, all confirming the suitability of the drug for the treatment of PAH following either the subcutaneous, IV, inhaled (as treprostinil sodium), or oral (as treprostinil diethanolamine) routes of administration.

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induced concentration-dependent relaxation of rabbit isolated, precontracted, mesenteric arteries and inhibition of adenosine diphosphate-induced platelet aggregation in human and rat platelet-rich plasma. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, thereby increasing cardiac output and stroke volume. Prostacyclins lower pulmonary artery pressure, increase cardiac output without affecting the heart rate (HR), and improve systemic oxygen transport as well as possibly reversing pulmonary artery remodeling. There is also increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells may contribute, along with vasodilation, to the therapeutic effects of PGI_2 in the treatment of PAH. The mechanism of action is therefore likely to be multifactorial.

1.2.2 General Toxicology

1.2.2.1 Active Pharmaceutical Ingredient: Treprostinil

A well-defined clinical safety profile exists for treprostinil sodium; acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies have been performed in both rats and dogs and support the chronic administration to patients (Remodulin Package Insert 2018, Tyvaso Package Insert 2017).

The toxicokinetic profile of treprostinil was also evaluated in acute and repeat-dose toxicity studies of up to 13 weeks in duration in rodents and dogs, which supported the chronic administration of inhaled treprostinil to patients. In addition, a 2-year rat carcinogenicity study was performed with treprostinil for inhalation at target doses up to 5.25, 10.6, and 34.1 µg/kg/day, which found no evidence for carcinogenic potential associated with inhaled

treprostinil in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 µg.

1.2.3 Clinical Experience

1.2.3.1 Inhaled Treprostinil (Tyvaso)

A series of acute and chronic investigator-initiated clinical studies were conducted with inhaled treprostinil to optimize the formulation for inhalation; determine dose response, tolerability, and safety; and also to evaluate safety and tolerability when combined with other PAH therapies (Channick 2006, Voswinckel 2006). In the acute dosing studies, administration of inhaled treprostinil resulted in pulmonary vasodilation at relatively low doses. In the chronic studies, administration of inhaled treprostinil resulted in sustained improvement of exercise capacity.

A randomized, double-blind, placebo-controlled, Phase 3 study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil in combination with approved PAH therapies. Two hundred thirty-five subjects who were clinically stable on an approved background oral PAH therapy (bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by 6-Minute Walk Distance (6MWD). At Week 12, subjects receiving inhaled treprostinil had a median improvement of +21.6 m in 6MWD, and subjects in the placebo group had a median improvement of +3.0 m. The Hodges-Lehmann placebo-corrected median change from baseline in peak 6MWD was +20.0 m (p=0.00044). The durability of this result was supported by secondary measures related to the trough 6MWD, which was measured at least 4 hours after the last dose of inhaled treprostinil. At Week 12, trough 6MWD showed a placebo-corrected median treatment effect of 13.7 m (p=0.0066). The most commonly reported adverse events (AEs) in the inhaled treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment-related changes in chest x-rays, pulmonary function tests (PFTs), or clinical laboratory parameters (McLaughlin 2010).

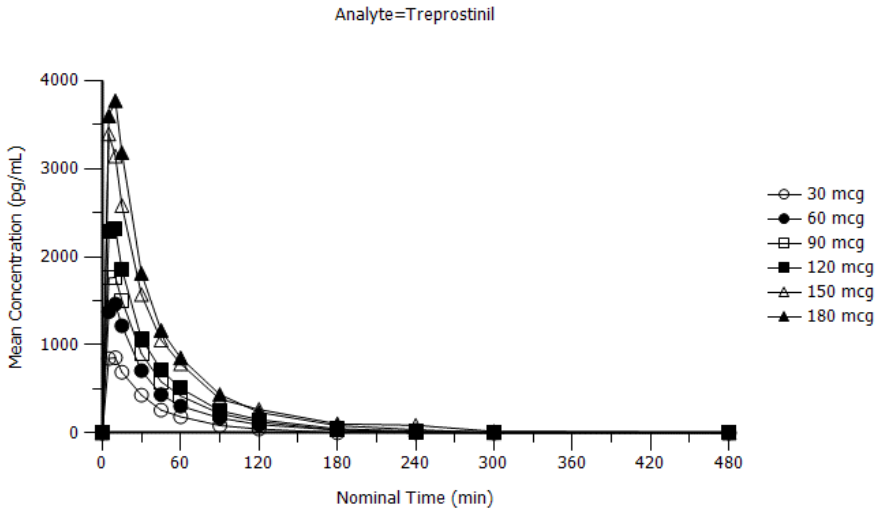
An open-label, extension study of the TRIUMPH-I study to evaluate the use of long-term inhaled treprostinil therapy was also conducted (TRIUMPH-OL). Subjects received 1 to 12 breaths (6 to 72 µg) 4 times daily (QID) to achieve daily doses of 24 to 288 µg. The longest duration of

inhaled treprostinil exposure in the open-label study was 5.4 years and the mean duration 2.3 years. There were observed improvements in median 6MWD at 6, 12, 18, and 24 months of 28, 31, 32, and 18 m, respectively. These data support the durability of improvement in 6MWD obtained with inhaled treprostinil as demonstrated during the double-blind phase of the study. Therapeutic benefit was also noted with improvements in the Borg dyspnea score, New York Heart Association Functional Classification, and quality of life. Survival was robust with 1- and 2-year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the study. The most frequently reported AEs during the open-label study were cough (39%), headache (31%), upper respiratory tract infection (22%), and nausea (22%). There were no clinically significant changes in clinical chemistry or hematology parameters. Unique findings that related to the inhaled route of administration, in addition to cough, were throat pain and throat irritation, occurring in 12% and 10% of subjects, respectively. These events were usually of mild or moderate severity and transient in duration. In a few subjects, these specific AEs were more pronounced as 6 subjects (3%) discontinued inhaled treprostinil due to cough, including 1 subject (<1%) with dry throat.

1.2.3.2 Treprostinil Inhalation Powder

An open-label, single ascending dose (SAD) study in healthy normal volunteers, MKC-475-001, was conducted to assess the safety and tolerability of TreT. A total of 36 healthy volunteers were sequentially assigned to 6 cohorts (6 subjects per cohort) of ascending dose levels of TreT (30, 60, 90, 120, 150, and 180 µg). Each subject received 1 dose of TreT by oral inhalation during the Treatment Period. The incidence and severity of AEs were assessed and pharmacokinetic (PK) parameters were measured by analyzing plasma concentrations of treprostinil. Bioanalysis data confirmed treprostinil plasma concentrations and exposure at clinically relevant concentrations when TreT is administered as a dry powder via oral inhalation. Treprostinil exposure, as measured by maximal drug concentration (C_{max}) and area under the curve (AUC), increased in a linear manner with increasing dose up to 180 µg tested, which would correspond to a 30-breath dose of Tyvaso.

Figure 1-1 Mean Plasma Treprostinil Concentration-time Profiles after Single-dose Administrations of 30 µg to 180 µg Treprostinil Inhalation Powder (TreT)



The most frequently reported AEs overall were cough (31%) and headache (22%). There were no severe AEs, serious AE (SAEs), or deaths during this study. No AEs led to a subject's early termination. No clinically significant abnormalities on oropharyngeal examinations, clinical laboratory evaluations, electrocardiograms (ECGs), or PFTs (spirometry) were observed. Overall, TreT was safe and well tolerated as oral inhalation doses of 30, 60, 90, 120, and 150 µg.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

UTC is developing a combination drug-device product which is comprised of a dry powder formulation of TreT and a small, portable, dry powder inhaler. This combination product is a change in dosage form for treprostinil from a solution for oral inhalation (Tyvaso) to a dry powder for oral inhalation. The dry powder contains the inhalation excipient, FDKP, which is an excipient present in Afrezza, an FDA-approved drug product that is listed in the FDA Inactive Ingredient Database. The properties of the dry powder are suitable for dosing by oral inhalation (eg, particle size suitable for pulmonary delivery). The device is a reusable, breath-powered, dry powder inhaler that does not require software, electrical power, or cleaning. For these reasons, it

is significantly smaller and more portable than the currently available inhaled prostacyclin therapies.

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that the systemic exposure, PK, and tolerability of treprostinil will be similar in patients with PAH when administered as TreT and Tyvaso.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this clinical study is to evaluate the safety and tolerability of TreT in subjects with PAH currently treated with Tyvaso.

2.2 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 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 PQ-ITD and patient-reported PAH symptoms and impact with the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) Questionnaire.

3 EXPERIMENTAL PLAN

3.1 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 QID) will take a dose of Tyvaso in the clinic and undergo PK assessments, safety assessments, and a 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.

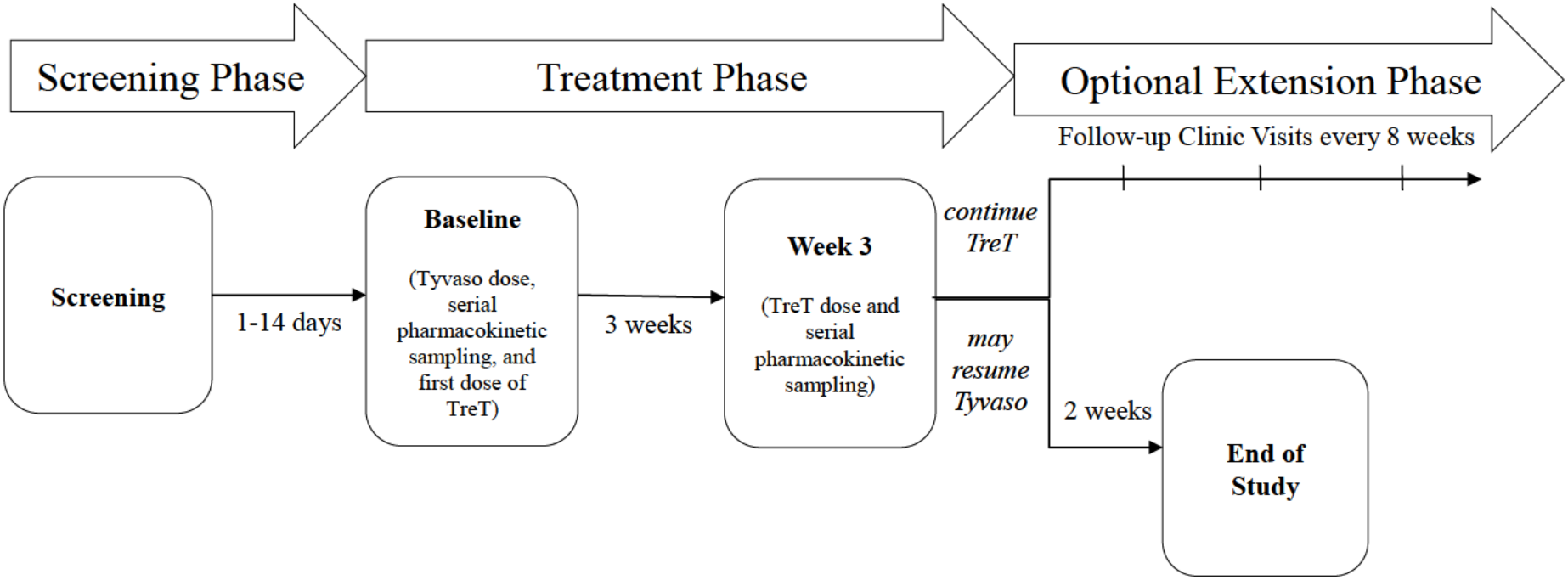
Screening Phase: Prospective subjects will be assessed during the Screening Phase to determine eligibility for the study. The Screening Visit must occur within 14 days prior to Baseline. During this Screening Phase, eligible subjects will sign the Informed Consent Form (ICF) and undergo screening assessments. 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 6-Minute Walk Test (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 (PE), 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.

Figure 3-1 Study Flow Chart



3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Times and Events

Study Phase		Combined Screening & Baseline[a,b]	Treatment Phase		End of Study/Early Termination Visit[c,k]	Optional Extension Phase[d]
Study Visit	Screening[a]		Baseline[b]	Week 3[c]		Week 11 then every 8 weeks[d]
Study Day	-14 to -1	1	1	21		
Informed Consent	X	X				
Inclusion/Exclusion Criteria	X	X	X			
PQ-ITD[m]		X	X	X	X	
PAH-SYMPACT[m]		X	X	X	X	X
Inspiratory Criteria Assessment	X	X	X			
Demographics	X	X				
Medical History	X	X				
Physical Examination	X	X	X	X	X	X
Vital Signs[e]	X	X	X	X	X	X
Urine Pregnancy Test[h]	X	X	X	X	X	X
Clinical Laboratory Assessments		X	X	X	X	X
12-lead ECG[n]		X	X		X	
PK Blood Samples[j]		X	X	X		
Blood Sample for Biomarker Evaluation (Optional)[f]		X	X	X		X
Blood Sample for Whole Genome Sequencing (Optional)[g]		X	X			
6MWT[b]	X	X	X	X	X	X
Dosing Instructions/Dosing Diary/TreT Accountability		X	X	X	X[o]	X

Study Phase		Combined Screening & Baseline[a,b]	Treatment Phase		End of Study/Early Termination Visit[c,k]	Optional Extension Phase[d]
Study Visit	Screening[a]		Baseline[b]	Week 3[c]		Week 11 then every 8 weeks[d]
Telephone/Email Contact[l]		X	X	X		X
AEs/SAEs[i]	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X

Abbreviations: 6MWT, 6-Minute Walk Test; ECG, electrocardiogram; AE, adverse event; PK, pharmacokinetic; PAH-SYMPACT, Pulmonary Arterial Hypertension Symptoms and Impact; PQ-ITD, Preference Questionnaire for Inhaled Treprostinil Devices; SAE, serious adverse event; TreT, Treprostinil Inhalation Powder

a Screening Visit assessments can occur up to 14 days prior to the Baseline Visit. If subjects are able to satisfy all eligibility criteria on the same day, Screening assessments can be combined with baseline assessments.

b If the subject has not previously undergone a 6MWT at the study site on the course intended for use during the study, a practice test must be conducted at the Screening Visit and must precede the baseline 6MWT by at least 1 day. To assist with subject scheduling, the baseline 6MWT may be conducted within 24 hours prior to PK sampling (eg, previous day). If the baseline 6MWT is conducted the day prior to PK sampling, then the Week 3 6MWT must also be conducted on the day prior to PK sampling for consistency. If the 6MWT is conducted concurrently with the PK sampling, it should occur between 45 to 60 minutes after the most recent dose. If the Baseline 6MWT is conducted concurrently with PK sampling, then the Week 3 6MWT must also be conducted concurrently with PK sampling. All 6MWTs should be conducted between 10 to 60 minutes after the most recent dose. Prior to the start of each 6MWT, the subject should rest (seated) for at least 10 minutes.

c The visit window for the Week 3 Visit and the End of Study Visit is ±3 days.

d The visit window for the Optional Extension Phase Visits is ±5 days. If the subject consents to the Optional Extension Phase of the study, the study will continue with clinic visits every 8 weeks until the study is terminated for any reason or the drug/device becomes commercially available. Additional unscheduled visits may be scheduled as required, for example, to address AEs or to titrate doses as appropriate.

e Vital signs must be collected after 5 minutes of rest (seated); no other measurements or procedures should be performed during this 5-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, then they should be obtained after recovery from the 6MWT.

f For subjects consenting to the optional biomarker sample. For subjects continuing in the Optional Extension Phase, this sample is only required at Week 51 (or upon early termination if prior to Week 51).

g For subjects consenting to the optional whole genome sequencing sample.

h For women of childbearing potential.

i All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all End of Study Visit assessments have been completed and should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit.

j The in-clinic dose of Tyvaso or TreT will be inhaled in the clinic, followed by serial PK assessments (see Section 3.3.1.1 for details).

k If a subject elects to discontinue TreT at the end of the Treatment Phase, an End of Study Visit must be completed within 2 weeks (±3 days). If a subject is discontinued from the study prematurely, an Early Termination Visit should be completed as soon as possible. Subjects who permanently discontinue TreT are encouraged to undergo premature termination assessments prior to discontinuing TreT or as close as possible to the last dose of TreT.

l At least weekly telephone contact is required during the 3-week Treatment Phase. During the optional extension phase, telephone contact must occur at least every 2 weeks between Week 3 and Week 11, and must occur at least monthly after Week 11 to encourage uptitration in addition to assessing AEs and concomitant medications. Contact may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit. Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in the clinic for clinically significant AEs or other emergent issues.

m The PQ-ITD and PAH-SYMPACT should be completed as the first assessments during the visit before the subject completes any of the other scheduled visit assessments (after informed consent is obtained). The PQ-ITD for TreT will only be administered during an Early Termination Visit if the subject discontinues during the 3-week Treatment Phase. The PAH-SYMPACT will be conducted at Week 11 visit only in the Optional Extension Phase.

n The 12-lead ECG should be recorded after at least 5 minutes of rest.

o Only drug accountability and dosing diary will be performed at the End of Study Visit or Early Termination Visit.

Table 3-2 Schedule of Events for Dosing and Pharmacokinetic Sampling - Baseline and Week 3 Visit

Time Relative to Dose (minutes)	Activity[a]
-15±3 (predose)	PK Sample 1
0 (dose)	Administer dose
5±3	PK Sample 2
10±3	PK Sample 3
15±3	PK Sample 4
30±3	PK Sample 5
45±3	PK Sample 6
90±3	PK Sample 7
120±3	PK Sample 8
180±3	PK Sample 9
240±3	PK Sample 10
300±3	PK Sample 11

Abbreviations: 6MWT, 6-Minute Walk Test; PK, pharmacokinetic

a If the baseline 6MWT is conducted concurrently with the PK sampling, then the Week 3 6MWT must also be conducted concurrently with PK sampling. If the 6MWT is conducted concurrently with the PK sampling, it should occur between 45 to 60 minutes after the most recent dose.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy Assessments

3.3.1.1 Pharmacokinetic Assessments

Fifteen minutes prior to administration of the in-clinic dose of Tyvaso or TreT at the Baseline Visit and the Week 3 Visit, qualified study personnel, as delegated by the Investigator, will obtain a predose blood sample of approximately 5 mL via an indwelling IV catheter or by direct venipuncture. The predose sample should occur at least 4 hours after the subject's last dose of Tyvaso or TreT. Subsequent serial blood samples of approximately 5 mL will be taken in a similar manner at the following timepoints (±3 minutes): 5, 10, 15, 30, 45, 90, 120, 180, 240, and 300 minutes after Tyvaso or TreT administration (see Table 3-2). Blood samples will be analyzed for treprostinil plasma concentrations.

3.3.1.2 6-Minute Walk Test

The 6MWT is a validated and reliable measure of exercise capacity in patients with chronic respiratory diseases (Holland 2014). This study will utilize an unencouraged 6MWT to minimize potential bias associated with encouragement. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements as described in Appendix 15.1. Subjects who have not previously performed the 6MWT at the study site on the course intended for use during the study must perform a practice 6MWT at the study site at least 1 day prior to the Baseline Visit. Subjects will perform a peak 6MWT at Baseline to confirm their eligibility to participate in the study (6MWD ≥150 m per Inclusion Criterion 7). Prior to the start of each 6MWT, the subject must rest (seated) for at least 10 minutes. To assist with subject scheduling, the baseline 6MWT may be conducted within 24 hours prior to PK sampling (eg, previous day). If the baseline 6MWT is conducted the day prior to PK sampling, then the Week 3 6MWT must also be conducted on the day prior to PK sampling for consistency. Peak 6MWTs will be conducted at study visits as specified in Table 3-1. All 6MWTs should be conducted between 10 to 60 minutes after the most recent dose of Tyvaso or TreT. If the 6MWT is conducted concurrently with the PK sampling, the 6MWT should occur between 45 to 60 minutes after the most recent dose. Subjects receiving supplemental oxygen during the Baseline 6MWT should continue to receive the same flow rate at the Week 3 6MWT. Pulmonary rehabilitation

may not be introduced to a subject's treatment regimen within 12 weeks prior to Baseline through the Week 3 Visit.

3.3.1.3 Preference Questionnaire for Inhaled Treprostinil Devices

The Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD) will be administered at the Baseline Visit to assess the subject's current use of the Tyvaso Inhalation System and at the Week 3 Visit or the Early Termination Visit to assess the subject's use of the TreT Inhaler. The PQ-ITD for TreT will only be administered during an Early Termination Visit if the subject discontinues during the 3-week Treatment Phase. The PQ-ITD should be completed as the first assessment during the visit before the subject completes any of the other scheduled visit assessments. Copies of the PQ-ITD (Tyvaso and TreT versions) can be found in the Study Reference Manual and will only be administered at study sites where available.

3.3.1.4 PAH-SYMPACT Questionnaire

The PAH-SYMPACT is a patient reported outcome (PRO) questionnaire consisting of 11 symptom and 11 impact items, which was developed based on interviews of PAH patients and following PRO guidance from the US Food and Drug Administration (FDA) (McCollister 2016, Chin 2018).

The PAH-SYMPACT questionnaire will be administered at the Baseline Visit, Week 3 Visit, and the Week 11 Visit (subjects participating in the Optional Extension Phase) or the Early Termination Visit. Detailed instructions on how to administer the PAH-SYMPACT to subjects will be provided to the sites. A copy of the PAH-SYMPACT questionnaire can be found in the Study Reference Manual and will only be administered at study sites where available.

3.3.1.5 Optional Biomarker and Optional Whole Genome Sequencing

For subjects consenting to the optional biomarker sample, blood will be collected for the evaluation of biomarkers (specific targets to be determined) at Baseline, Week 3 Visit, and at the Week 51 Visit for subjects participating in the Optional Extension Phase (or upon early termination if prior to Week 51). These samples will be shipped to the central laboratory for processing and storage prior to analysis.

For subjects consenting to whole genome sequence analysis, a blood sample will be collected at Baseline. These samples will be shipped to the central laboratory for processing and storage prior to analysis. Whole genome sequences will be analyzed for genetic markers that may be associated with clinical response and tolerability.

Samples for the optional biomarker and optional whole genome sequencing will be coded in a manner that allows them to be matched to a study site and/or a subject number, but will not carry personal identifiers that could be traced to a specific individual. Complete instructions regarding the processing, packaging, and shipping of samples will be provided in a separate laboratory manual.

3.3.2 Safety and Tolerability Assessments

Safety assessments include incidence and severity of reported AEs, as well as changes from screening in vital signs, clinical laboratory tests, ECGs, and PEs.

3.3.2.1 Inspiratory Criteria Assessment

The subject's ability to perform inhalation maneuvers will be assessed at the Screening Visit and the Baseline Visit. Subjects must be able to perform inhalation maneuvers using the BluHale® technology that meets inspiratory training criteria. Subjects who are not able to demonstrate proper technique will be considered screen failures.

3.3.2.2 Medical History and Physical Examinations

A complete medical history (including pulmonary hypertension history), demographics, and PE (including an oropharyngeal exam) will be conducted during the Screening Visit. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs should be recorded. Any significant changes to the subject's medical condition and physical examination must be documented throughout the course of the study. A complete PE will be conducted by appropriate study personnel at the Screening Visit, Baseline Visit, Week 3 Visit, and the Early Termination Visit. For subjects continuing in the Optional Extension Phase, a physical exam will conducted at each Extension Visit. Any clinically significant changes from Baseline noted during the study should be reported as AEs.

3.3.2.3 Vital Signs

Vital signs will be assessed at study visits as specified in Table 3-1. Vital signs measured will include blood pressure (systolic and diastolic), HR, respiratory rate (RR), and weight. Vital signs must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures should be performed during this 5-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, then they should be obtained after recovery from the 6MWT. Vital signs should also be assessed and reported in the case of abnormal clinical signs and symptoms.

3.3.2.4 12-Lead Electrocardiogram

A 12-lead ECG will be recorded after at least 5 minutes of rest at the Baseline Visit and End of Study Visit or Early Termination Visit. Recordings should include lead II as a rhythm strip and contain at least 5 QRS complexes. ECG parameters to be collected include rhythm, HR, PR interval, QT interval, QRS duration (uncorrected), and any clinically significant abnormalities.

3.3.2.5 Clinical Laboratory Assessments

Clinical laboratory assessments will be collected at the Baseline Visit, Week 3 Visit, End of Study Visit or Early Termination Visit, and at follow-up visits in the Optional Extension Phase as specified in Table 3-1. Clinical laboratory results outside the normal reference range must be assessed for clinical significance by the Investigator. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status. Clinically significant abnormal laboratory test values will be reported as AEs and treated and/or followed-up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator. Where appropriate, medical tests and examinations will be performed to assess and document resolution.

3.3.2.5.1 Clinical Chemistry and Hematology

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

Table 3-3 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

3.3.2.5.2 Pregnancy Testing

Women of childbearing potential (WOCBP) will undergo a urine pregnancy test at study visits as specified in Table 3-1. A positive pregnancy test will exclude the subject from further participation in the study. Pregnant subjects who are discontinued from the study will be transitioned to an alternate therapy at the discretion of the Investigator.

3.3.2.6 Adverse Events

AEs will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, or until the subject is either discontinued from the study or all End of Study Visit assessments have been completed. Each subject will be questioned for AEs at each scheduled study visit. Subjects will also be instructed to spontaneously report all AEs throughout the study.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for serious (ie, serious AEs [SAEs]) should be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final study visit (End of Study Visit or Early Termination Visit). All AEs/SAEs that occur while the subject is in study will be recorded as instructed in this protocol.

Sections 9 and 15.2 provide the guidelines and definitions for recording AEs.

3.3.2.7 Concomitant Medications

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events as well as vitamins and herbal supplements, should be recorded in

the subject's source documents and captured in the electronic Case Report Form (eCRF) as required.

3.3.2.8 Periodic Telephone/Email Contact

At least weekly telephone contact is required throughout the Treatment Phase to assess for AEs and concomitant medications. During the Optional Extension Phase, telephone contact must occur at least every 2 weeks between Week 3 and Week 11, and must occur at least monthly after Week 11 to encourage uptitration in addition to assessing AEs and concomitant medications. These contacts may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit. The subject may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in the clinic for clinically significant AEs or other emergent issues. A copy of the emails and/or telephone contact sheets (ie, AEs reported and/or concomitant medication changes) must be documented in the subject's source documentation.

3.4 NUMBER OF CENTERS

This study is multicenter with approximately 15 participating study centers.

3.5 NUMBER OF SUBJECTS

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

3.6 ESTIMATED STUDY DURATION

The mandatory portion of the study is expected to be a minimum of 5 weeks duration. If the subject consents to the Optional Extension Phase of the study, the study will continue with clinic visits every 8 weeks until the study is terminated for any reason or the drug/device becomes commercially available.

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

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

1. Subject voluntarily gives informed consent to participate in the study.
2. Subject is aged 18 years or older at the time of signing informed consent.

3. WOCBP are those who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal (defined as amenorrhea for at least 12 consecutive months). WOCBP must be nonpregnant (as confirmed by a urine pregnancy test at Screening prior to initiating study medication), nonlactating, and will do 1 of the following:
    a. Abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
    b. Use 2 medically acceptable, highly effective forms of contraception for the duration of study, and at least 30 days after discontinuing TreT. Medically acceptable, highly effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), intrauterine devices or systems, and barrier methods (such as a condom or diaphragm) when used with a spermicide.
4. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing TreT.
5. Subject is diagnosed with PAH as defined by the following World Health Organization (WHO) Group 1 categories:
    a. Idiopathic/familial
    b. Associated with unrepaired or repaired congenital systemic-to-pulmonary shunts (repaired ≥5 years prior to screening)
    c. Associated with collagen vascular disease
    d. Associated with human immunodeficiency virus
    e. Associated with appetite suppressant/other drug or toxin use
6. Subject must have started Tyvaso ≥3 months prior to the Baseline Visit and must currently be on a stable regimen (no change in dose within 30 days of Baseline Visit) of Tyvaso (6 to 12 breaths QID).
7. Baseline 6MWD ≥150 m.
8. If currently receiving other approved background therapy (eg, ERA or PDE5-I or both), the subject must be on a stable dose with no additions or discontinuations for a minimum of 30 days prior to Screening.
9. The subject has had evidence of forced expiratory volume in 1 second (FEV_1) ≥60% and FEV_1/forced vital capacity ratio ≥60% during the 6 months prior to enrollment.
10. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing, and likely to be cooperative with protocol requirements, including all study visits.

4.2 EXCLUSION CRITERIA

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

1. Subject is pregnant or lactating.
2. Subject has been diagnosed with pulmonary hypertension for reasons other than WHO Group 1 as outlined in Inclusion Criterion 5 (including but not limited to portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, hemolytic anemia, sarcoidosis).
3. Subject has a history of uncontrolled sleep apnea, parenchymal lung disease, or hemodynamically significant left-sided heart disease (including but not limited to aortic or mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, or coronary artery disease).
4. Subject is currently taking any other prostacyclin analogue or agonist, including but not limited to selexipag, epoprostenol, iloprost, or beraprost; except for acute vasoreactivity testing.
5. Subject experienced an acute exacerbation of disease or hospitalization for any reason within 30 days of the Screening Visit or between Screening and Baseline.
6. Subject is WHO Functional Class IV at Screening.
7. Subject has used any investigational drug/device or participated in any other investigational study with therapeutic intent within 30 days prior to the Screening Visit.
8. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant idiosyncratic reaction to treprostinil or excipients in the investigational product.
9. Subject has conditions that, in the opinion of the Investigator, would make the subject ineligible.
10. Subject is not able to perform inhalation maneuvers that meet inspiratory training criteria.
11. Subject has a musculoskeletal disorder (eg, arthritis affecting the lower limbs, recent hip or knee joint replacement) or any disease that would likely be the primary limit to ambulation, or is connected to a machine that is not portable enough to allow for a 6MWT.
12. Subject has had a new type of chronic therapy (including but not limited to oxygen, a different class of vasodilator, diuretic, and digoxin) for pulmonary hypertension added within 30 days of the Screening Phase.
13. Initiation of pulmonary rehabilitation within 12 weeks prior to the Baseline Visit.

4.3 PRESCRIBED THERAPY

Subject must have started Tyvaso ≥3 months prior to the Baseline Visit and must currently be on a stable regimen (no change in dose within 30 days of Baseline Visit) of Tyvaso (6 to 12 breaths QID). Subjects must not be receiving any other prostacyclin analogue or agonist, including but not limited to selexipag, epoprostenol, iloprost, or beraprost, except for Tyvaso within 30 days prior to the Baseline Visit (unless used for acute vasoreactivity testing) until study termination. Subjects on any other FDA-approved PAH background therapy (eg, ERA, PDE5-I, and/or sGC stimulator) must be on a stable and optimized dose for ≥30 days prior to the Baseline Visit. Subjects may not newly initiate or discontinue PAH background therapy from the Screening Phase through the Week 3 Visit.

4.3.1 Concomitant Medications

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events as well as vitamins and herbal therapies, should be recorded in the subject's source documents and transcribed into the eCRF as required.

4.3.2 Other Treatments

Subjects may not initiate pulmonary rehabilitation within 12 weeks prior to Baseline through the Week 3 Visit.

5 SUBJECT ENROLLMENT

All subjects who sign the ICF will be assigned a subject number consisting of the site number followed by an unique consecutive number within each site.

5.1 TREATMENT ASSIGNMENT

Subjects will be assigned treatment with TreT based on current Tyvaso regimen as detailed in Section 6.1.2. 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.

6 DRUGS AND DOSING

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

6.1.1 Tyvaso

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via ultrasonic nebulization using the commercially available Tyvaso Inhalation System, which emits a dose of approximately 6 µg per breath. All subjects will receive their current dose of Tyvaso in the clinic at the Baseline Visit for the 6MWT and PK sampling.

6.1.2 Treprostinil Inhalation Powder

During the Treatment Phase, TreT will be supplied in single-use cartridges that contain either 32 µg or 48 µg of treprostinil per cartridge. All subjects will initiate TreT at a dose corresponding to their current Tyvaso regimen per Table 6-1. Subjects will be trained on inhalation of TreT using the inhaler device. Detailed instructions for the use of this device will be provided to all study subjects. In addition, all subjects will receive a copy of the TreT Instructions for Use.

Table 6-1 Treatment Phase Assignments

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

Abbreviations: QID, 4 times daily; TreT, Treprostinil Inhalation Powder

A single-use cartridge is manually inserted into the dry powder inhaler, which is a proprietary, breath-activated, reusable, dry powder inhaler that will deliver TreT to the lungs. Powder is discharged from the inhaler when the subject inhales. Each subject will be trained on inhalation technique prior to the first dose of TreT in clinic. Additionally, subjects must be able to perform inhalation maneuvers using the BluHale technology that meets inspiratory training criteria. Subjects who are not able to demonstrate proper technique will be considered screen failures.

At the end of the Treatment Phase, subjects will be offered the opportunity to continue therapy with TreT or resume Tyvaso therapy. If the subject continues therapy with TreT 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. During the Optional Extension Phase, a 64 µg cartridge strength may be dispensed as appropriate to meet dosing requirements. Dose titration may start at the Week 3 Visit after all study assessments have been completed and subject agrees to participate in the Optional Extension Phase.

6.2 COMPLIANCE

Each subject will be provided with a dosing diary in order to record dosing information from Baseline Visit through End of Study Visit. Subjects will be asked to return the completed dosing diary, all used and unused TreT cartridges, and all TreT inhalers to each scheduled study visit. At each visit, all TreT cartridges and inhalers returned by the subject (used and unused) will be collected and new TreT cartridges and inhalers will be dispensed. The appropriate study personnel must document the number of used and unused cartridges and determine if the appropriate amount of TreT cartridges remain based on the dose of TreT prescribed.

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each study visit, the subject will be asked whether he or she has been compliant with dosing instructions. If it is determined that a subject is not compliant with TreT, then site personnel must re-educate the subject on proper doing compliance and its importance. Continued noncompliance during any phase of the study may lead to withdrawal of the subject from the study after consultation between the Investigator and the Sponsor.

7 EXPERIMENTAL PROCEDURES

Assessments during the study will be performed according to Table 3-1. Screening may begin up to 14 days prior to the Baseline Visit. If subjects are able to satisfy all eligibility criteria on the same day, a combined Screening/Baseline Visit may be conducted.

7.1 SCREENING VISIT

The recommended sequence of assessments for the Screening Visit is as follows:

- Informed consent
- Inclusion/exclusion review
  - If necessary to satisfy inclusion criterion #9, procedures may be performed to provide evidence of FEV_1 ≥60% and FEV_1/forced vital capacity ratio ≥60%.
- Inspiratory criteria assessment

- Demographics
- Medical history (including PH history)
- Physical exam
- Vital signs (following at least 5 minutes of rest) including weight, RR, HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP)
- Urine pregnancy test for WOCBP
- Practice 6MWT (only required if the subject has not previously performed a 6MWT at the study site on the study course; must precede the baseline 6MWT by at least 1 day; to be conducted following at least 10 minutes of rest [sitting])
- AE assessment
- Concomitant medications

7.2 BASELINE VISIT

Baseline Visit activities will include the following:

- Administration of PQ-ITD (Tyvaso Inhalation System assessment)
- Administration of PAH-SYMPACT Questionnaire
- Confirmation of inclusion/exclusion criteria
- Inspiratory criteria assessment
- Physical examination
- Vital signs (following at least 5 minutes of rest); including weight, RR, HR, SBP, and DBP
- Urine pregnancy test for WOCBP
- Blood draws for clinical laboratory parameters
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- 12-lead ECG (following at least 5 minutes of rest)
- In-clinic dose of Tyvaso
- Peak 6MWT (should be conducted between 10 to 60 minutes after the most recent dose and following at least 10 minutes of rest [sitting]; if the 6MWT is conducted concurrently with the PK sampling, the 6MWT should occur between 45 to 60 minutes after the most recent dose; to assist with subject scheduling, the baseline 6MWT may be conducted within 24 hours prior to PK sampling [eg, previous day])
- PK blood samples (see Table 3-2 for specific timepoints; the first sample is a predose sample and should occur at least 4 hours after the subject's last dose of Tyvaso)
- AE assessment
- Concomitant medications
- Dosing instructions/dosing diary/TreT accountability
- First dose of TreT

7.3 COMBINED SCREENING AND BASELINE VISIT

If subjects are able to satisfy all eligibility criteria on the same day, a combined Screening/Baseline Visit may be conducted. The recommended sequence of assessments for the Combined Screening and Baseline Visit is as follows:

- Informed consent
- Administration of PQ-ITD (Tyvaso Inhalation System assessment)
- Administration of PAH-SYMPACT Questionnaire
- Inclusion/exclusion review
- Inspiratory criteria assessment
- Demographics
- Medical history (including PH history)
- Physical exam
- Vital signs (following at least 5 minutes of rest) including weight, RR, HR, SBP, and DBP
- Blood draws for clinical laboratory parameters
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- Urine pregnancy test for WOCBP
- 12-lead ECG (following at least 5 minutes of rest)
- In-clinic dose of Tyvaso
- Peak 6MWT (should be conducted to confirm eligibility and prior to enrollment; should be conducted between 10 to 60 minutes after the most recent dose and following at least 10 minutes of rest [sitting]; if the 6MWT is conducted concurrently with the PK sampling, the 6MWT should occur between 45 to 60 minutes after the most recent dose; to assist with subject scheduling, the baseline 6MWT may be conducted within 24 hours prior to PK sampling [eg, previous day])
- PK blood samples (see Table 3-2 for specific timepoints; the first sample is a predose sample and should occur at least 4 hours after the subject's last dose of Tyvaso)
- AE assessment
- Concomitant medications
- Dosing instructions/dosing diary/TreT accountability
- First dose of TreT

7.4 WEEK 3 VISIT

Week 3 Visit activities will include the following:

- Administration of PQ-ITD (TreT assessment)

- Administration of PAH-SYMPACT Questionnaire
- Physical examination
- Urine pregnancy test for WOCBP
- Vital signs (following at least 5 minutes of rest); including weight, RR, HR, SBP, and DBP
- Blood draws for clinical laboratory parameters
- Collection of blood sample for evaluation of biomarkers (optional)
- In-clinic dose of TreT
- Peak 6MWT (should be conducted between 10 to 60 minutes after the most recent dose and following at least 10 minutes of rest [sitting]; if the 6MWT is conducted concurrently with the PK sampling, the 6MWT should occur between 45 to 60 minutes after the most recent dose)
- PK blood samples (see Table 3-2 for specific timepoints; the first sample is a predose sample and should occur at least 4 hours after the subject's last dose of TreT)
- Dosing instructions/dosing diary/TreT accountability
- AE assessments
- Concomitant medications

7.5 END OF STUDY VISIT AND/OR EARLY TERMINATION VISIT

If a subject elects to discontinue TreT at the end of the Treatment Phase, an End of Study Visit must be completed within 2 weeks (±3 days). If a subject is discontinued from the study prematurely, an Early Termination Visit should be completed as soon as possible. Subjects who permanently discontinue TreT are encouraged to undergo premature termination assessments prior to discontinuing TreT or as close as possible to the last dose of TreT. The following activities will be performed:

- Administration of PQ-ITD (TreT assessment; only for subjects that discontinue during the 3-week Treatment Phase)
- Administration of PAH-SYMPACT Questionnaire
- Physical examination
- Vital signs (following at least 5 minutes of rest), including weight, RR, HR, SBP, and DBP
- Urine pregnancy test for WOCBP
- Blood draws for clinical laboratory parameters
- 12-lead ECG (following at least 5 minutes of rest)
- Peak 6MWT (should be conducted between 10 to 60 minutes after the most recent dose and following at least 10 minutes of rest [sitting])

- Dosing diary/TreT accountability
- AE assessment
- Concomitant medications

7.6 OPTIONAL EXTENSION PHASE VISITS

Subjects who choose to continue TreT and enter the Optional Extension Phase will complete study visits every 8 weeks. The assessments performed during the Optional Extension Phase will alternate as follows.

7.6.1 Week 11 Visit (Then Every 8 weeks)

Beginning on Week 11, the following assessments will be performed every 8 weeks:

- Administration of PAH-SYMPACT Questionnaire **(Week 11 only**)
- Physical examination
- Vital signs (following at least 5 minutes of rest), including weight, RR, HR, SBP, and DBP
- Urine pregnancy test for WOCBP
- Blood draws for clinical laboratory parameters
- Peak 6MWT (should be conducted between 10 to 60 minutes after the most recent dose and following at least 10 minutes of rest [sitting])
- Collection of blood sample for evaluation of biomarkers (optional) **(Week 51 only)**
- Dosing instructions/dosing diary/TreT accountability
- AE assessments
- Concomitant medications

7.6.2 TreT Dose Titration Visits

Dose 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. Titration may occur at a scheduled Extension Visit, or may occur at an unscheduled visit as deemed clinically appropriate by the Investigator.

7.6.3 TreT Blister Packaging

Once available, study drug will be provided as blister packages during the Optional Extension Phase. Subjects who are enrolled in the Optional Extension Phase will attend their subsequent Extension Visit as scheduled and will be resupplied with the blister-packaged study drug in place of the investigational foil pouch packaging. A 64 µg cartridge will be made available in addition

to the 32 µg and 48 µg cartridges, and may be dispensed as appropriate to meet dosing requirements. Once a subject is receiving study drug in the blister packaging, subsequent Extension Visits will occur every 8 weeks.

7.7 STUDY CONTACTS

At least weekly telephone contact is required throughout the Treatment Phase to assess for AEs and concomitant medications. During the Optional Extension Phase, telephone contact must occur at least every 2 weeks between Week 3 and Week 11, and must occur at least monthly after Week 11 to encourage uptitration in addition to assessing AEs and concomitant medications. These contacts may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit. The subject may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in the clinic for clinically significant AEs or other emergent issues. A copy of the emails and/or telephone contact sheets (ie, AEs reported and/or concomitant medication changes) must be documented in the subject's source documentation.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or be withdrawn from the study and/or TreT by the Investigator at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue TreT to protect the safety of the subject.
- The subject consistently deviated from the protocol.
- The subject has a lung transplant.
- The subject becomes pregnant.
- The subject's behavior is likely to undermine the validity of his/her results.

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF and an Early Termintion Visit should be completed as soon as possible. If TreT has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues TreT prematurely due to an AE, the subject will be followed until either the Investigator determines

that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 30 days if the AE extends beyond the final visit.

If a subject withdraws consent from either the optional biomarker and/or whole genome sequencing and/or requests sample destruction, the investigator must document the request and inform the Sponsor. The Sponsor will only keep data that are collected or generated up to the point at which consent to use the sample is withdrawn by the subject. Withdrawal of consent from the optional biomarker and/or optional whole genome sequencing does not affect consent to participate in any part of the analysis for which the subject has not withdrawn consent, nor does it affect consent to participate in the main clinical study.

8.2 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of the Investigator and/or Sponsor, continuation of the study represents a serious medical risk to the subjects or if the drug/device becomes commercially available. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.3 CRITERIA FOR DISCONTINUING THE SITE

The study may also be terminated at a given center if:

- The Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the site
- US FDA, European, or other national regulations are not observed
- The protocol is violated
- Changes in personnel or facilities adversely affect performance of the study.

9 ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical experience occurring to a subject during the clinical study whether or not it is related to the study drug.

An AE may include any of the following:

- An intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance.
- A worsening of existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (eg, exacerbation of a pre-existing illness following the start of the study or an increase in frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by the use of the term "adverse event."

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an AE.
- Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not AEs.
- Day-to-day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all End of Study Visit assessments have been completed.

9.1.2 Serious Adverse Event

An SAE is an AE occurring during the clinical study that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require medical/surgical intervention to prevent 1 of the

outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death.

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE, such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome, is also to be documented in the eCRF (see Section 9 and Appendix 15.2 for definitions). Where possible, AEs should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with any new or additional information as appropriate.

The inhaler to be used in this clinical study is identical in all aspects, including function, to the inhaler of the FDA-approved Afrezza drug-device combination product except for minor changes (these changes do not change drug delivery device performance). Any device complications associated with the use of the inhaler reported by the subject/health professional will be forwarded by UTC to the device manufacturer according to the specified timeline.

9.3 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

Sites should enter initial or follow-up SAE information regardless of causality or expectedness into the Sponsor's Electronic Data Capture (EDC) system (primary method) within 24 hours of awareness of SAE. The SAE will be directly transmitted from the EDC system to the Argus Safety Database. If the site is unable to enter the SAE electronically into the EDC system, the alternative for reporting is submitting the paper SAE Report Form via email to [redacted] or fax to [redacted] within 24 hours of awareness. If the paper SAE Report Form is submitted, the site will also be required to enter the SAE data into the EDC system. SAE source documents (eg, hospital discharge summary or death certificate) will be submitted by the site via email [redacted] or fax [redacted]. The Investigator or Sponsor (if appropriate) must also notify their Institutional Review Board (IRB), Independent Ethics Committee (IEC), and/or other local equivalent body of the reported SAE, including any follow-up information. Copies of each report and documentation of IEC/IRB/local equivalent body notification and receipt will be kept in the Clinical Investigator's study file.

9.4 SAFETY REPORTS

In accordance with national regulations, the Sponsor will notify the appropriate regulatory authority(ies) and all participating Investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or Ethics Committee (EC) in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

9.5 PREGNANCY

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification and Outcome Form and submitting via fax or e-mail to Global Drug Safety at UTC [redacted]) and withdraw the subject from the study. The United Therapeutics Global Drug Safety department will follow up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification Form. Pregnancy only becomes an AE/SAE if

there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion, or study discontinuation for any reason. A representative from the sponsor will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated, and the database will be edited as appropriate. The eCRF screens are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify his/her approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject's eCRF by the site after the Investigator initially signs the eCRF. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

Total sample size is planned to be 45 subjects. No formal sample size calculation has been conducted.

10.3 ANALYSIS PLAN

All PK and safety data will be listed and summarized in tables.

10.3.1 Pharmacokinetic Analysis

PK parameters of treprostinil (C_{max}, time of maximal plasma concentration, $t_{½}$, and AUC from time 0 to 300 minutes [AUC_{0-300}]) will be obtained from the resulting plasma drug concentration-time data. Plasma concentrations of treprostinil above the lower limit of quantitation will be used to calculate AUC_{0-300} and C_{max} for each treatment. PK parameters will be compared between Tyvaso and TreT and among all dose levels. PK parameters will be summarized using descriptive statistics.

10.3.2 Safety and Tolerability Analyses

The Safety Population will be defined as all subjects in the study who received at least 1 dose of TreT in the Treatment Phase. Safety analyses will be performed on the Safety Population. All AEs recorded by the Investigators will be assigned Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Terms by the Sponsor for reporting purposes.

The number and percent of subjects with AEs for each Treatment Phase will be tabulated by MedDRA System Organ Class and Preferred Term by relationship to treatment and severity. ECG and clinical laboratory test results will be summarized in shift tables. The original values and the changes from baseline in vital signs, laboratory parameters, and 6MWT results will be summarized with descriptive statistics.

10.4 INTERIM ANALYSIS

Interim analyses are not planned for this study.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the clinical study report.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

11.1.1 Study Drug

The Sponsor will supply study medication, TreT, as unit-dose cartridges. During the Treatment Phase of the study, 32 and 48 μg cartridges will be supplied in investigational foil pouches in cartons. One carton will contain 33 cartridges to provide 7 days of medication and 5 additional cartridges in the event the subject loses or damages a cartridge. Each carton will contain 1 strength of study medication.

During the Optional Extension Phase, the Sponsor will supply TreT cartidges in cartons with blister packaging. Each carton will contain 1 strength of study medication. During the Optional

Extension Phase, a 64 µg cartridge may be dispensed to meet dosing requirements as appropriate.

11.1.2 Study Device

The sponsor will supply dry powder inhalers that will be used in combination with the study drug cartridges. Each inhaler will be packaged individually in a clear plastic overwrap which will then be packaged in groups of 5 per carton. The inhaler will be provided with the instructions for use to assist the subjects in loading the cartridge and using the device properly.

Each subject will receive 1 carton of inhalers for the 3-week Treatment Phase of the study. Additional inhalers will be supplied for subjects remaining in the Optional Extension Phase.

11.2 LABELING

11.2.1 Study Drug

The primary packaging and outer carton will be labeled with but not limited to the product name, study number, kit identification number, date of manufacture, Sponsor's name and address, strength, and storage information (subject to regulatory requirements in each study region).

11.2.2 Study Device

Inhalers will be packaged in cartons, each containing 5 inhalers. The carton will be labeled with but not limited to the protocol name, study number, kit identification number, storage conditions, and the Sponsor's name and address.

11.3 STORAGE AND HANDLING OF CLINICAL STUDY MATERIAL

TreT will be supplied in individual cartridges packaged in sealed foil pouches during the Treatment Phase, and as blister packs during the Optional Extension Phase, once available. TreT should be stored at 2°C to 8°C (36°F to 46°F) prior to dispensing. Once dispensed to study subjects, TreT cartridges should be stored and used as directed by the study site. Cartridges should not be removed from their packaging until just prior to use (inhalation).

TreT inhalers are to be stored at ambient temperature during distribution and in-use period.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

Study sites will be supplied with a sufficient quantity of TreT cartridges and inhalers to begin enrollment in the study. An IRT will be utilized to assign each subject the appropriate study drug for the 3-week Treatment Phase and the Optional Extension Phase.

At each study visit for the duration of the study, all used and unused inhalers dispensed to a subject should be returned to the study site. During the Treatment Phase, all used and unused TreT cartridges should be returned to the study site. During the Optional Extension Phase, all blister packaging must be returned to the study site and used cartridges may be discarded after use.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for TreT accountability and reconciliation overall and on a per-subject basis. Drug accountability records are to be maintained during the study, and these records include, but are not limited to the amount of TreT received from the Sponsor, the amount dispensed to each subject, and the amount of used/unused TreT returned to the site by the subject.

At each visit, site personnel will:

- Collect and document all inhalers and all TreT cartridges and/or blister packaging returned by the subject (both used and unused).
- Compute study drug compliance using the dosing instructions given to the subject since the previous study visit and the amount of TreT cartridges and/or blister packaging returned.
- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

Once a representative from the Sponsor is able to confirm drug accountability for a completed subject, TreT cartidges and/or blister packaging will be returned to a Sponsor-designated location for destruction and/or destroyed onsite per institutional policy. All used and unused inhalers will be collected by the Sponsor for additional testing. In the event of device malfunction, at any point during the study, the inhalers should be returned to the Sponsor.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 US FDA REGULATORY REQUIREMENTS

The study will be conducted in accordance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and all applicable national regulations. The Sponsor will obtain the required approval from the FDA to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to the FDA and IRBs/ECs that require it. Any additional FDA reporting requirements, as specified by the FDA or IRB/EC, will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/EC-approved ICF prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject, and the original will be retained in the study site's records.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/IEC and provide the Sponsor with a copy of the approval letter. The IRB/IEC must also review and approve the study site's ICF and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/IEC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the ICF, the Investigator is responsible for obtaining IRB/IEC approval of these amended documents prior to implementation. Copies of the IRB/IEC correspondence and approval letters must be sent to the Sponsor.

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/IECs that require it.

A written summary of the study will be provided by the Investigator to the IRB/IEC following study completion or termination according to the IRB or IEC standard procedures. Additional updates will also be provided in accordance with the IRB/IEC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical study, at a minimum, the following documents will be provided to the site: Investigator's Brochure, clinical study protocol, ICF, Budget Agreement, and access to the eCRF.

At a minimum, the site will be required to provide the following documents to UTC or designee prior to study start: Signature page of the protocol, Form FDA 1572, Financial Disclosure Form(s), IRB/IEC Composition and Roster, IRB/IEC protocol and informed consent approval letters, and Curriculum Vitae of study staff listed on the 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. UTC, the FDA or other regulatory bodies, and the IRB/IEC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/IEC, or the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects, and any report published will not identify the subject's name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially affect the safety of participating subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria may be made only after consultation between UTC or its designee and the Investigator.

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/IEC prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/IEC for each study site.

At the end of the study, where applicable, a final report will be provided to the local regulatory agencies.

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify UTC before any disposal or change in location of study records.

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal regulations, ICH, and GCP guidelines, monitors for UTC or its designee will periodically contact the site and conduct on-site visits. During these visits, the monitor will at a minimum confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the monitor to discuss any findings or any relevant issues.

14 REFERENCES

ATS Statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111-117.

Channick RN, Olschewski H, Seeger W, et al. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. J Am Coll of Cardiol. 2006;48(7):1433-1437.

Chin KM, Gomberg-Maitland M, Channick RN, et al. Psychometric validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: results of the SYMPHONY trial. Chest. 2018;154(4):848-861.

Farber H and Loscalzo J. Mechanisms of disease: Pulmonary arterial hypertension. N Engl J Med. 2004;3511(16):1655-1665.

Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446.

McCollister D, Shaffer S, Badesch DB, et al. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) questionnaire: a new patient-reported outcome instrument for PAH. Respir Res. 2016;17(1):72.

McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010;55(18):1915-1922.

Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2018.

Rubin LJ. Primary pulmonary hypertension. N Engl J Med. 1997;336:111-117.

Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2017.

Voswinckel R, Ghofrani HA, Grimminger F, et al. Inhaled treprostinil [corrected] for treatment of chronic pulmonary arterial hypertension. Ann Intern Med. 2006;144(2):149-150.

15 APPENDICES

15.1 PROCEDURES FOR A 6-MINUTE WALK TEST

General Procedures

The 6MWT should be administered by the same tester at each study site throughout the study, whenever possible. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines and the usual practice of the investigative site (ATS Statement 2002). Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at the Week 3 6MWT.

The area used for the 6MWT should be pre-measured at approximately 30 m in length and at least 2 to 3 m in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested but the clock will continue to run. The subject may use ambulatory aids if needed. At the end of 6 minutes, the tester will call "stop where you are" while simultaneously stopping the watch and then measure the distance walked.

Instructions to the Subject

Subjects will be instructed that the preceding meal should be light. Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following **exact** dialogue with the subject:

> "The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say 'STOP,' please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"
"Start when I say 'GO.'"

The person administering the test will tell the subject the time at each minute by saying:

"You have 5 minutes to go."
"You have 4 minutes to go."
"You have 3 minutes to go."
"You have 2 minutes to go."
"You have 1 minute to go."

At 6 minutes, the person administering the test will tell the subject:

"Stop where you are."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

15.2 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Investigator or a designated member of his/her staff will probe each subject for any AEs that may have occurred. The Investigator should always ask the same question when conducting the verbal probe in order to ensure uniformity between subjects. The Investigator should ask:

"How are you doing (feeling)?"

Based on the subject's response to this question, the Investigator should ask additional questions relevant to the specific complaint such as:

"How severe is/was the symptom?"
"How often did the symptom occur?"
"How long did the symptom last?"

It is the Investigator's responsibility to review the results of all diagnostic and laboratory tests as they become available and ascertain if there is a clinically significant change from baseline. If the results are determined to be a clinically significant change from baseline, this should be reported as an AE. The Investigator may repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the abnormality should be used as the reported AE.

Using provided definitions, the Investigator will then:
(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

Definitions of Intensity, Seriousness, Causality, Action Taken, and Outcome

INTENSITY

An assessment of the relative intensity (severity) of an AE is based on the Investigator's clinical judgment. The maximum intensity encountered during the evaluation period should be checked. The assessment of intensity should be independent of the assessment of the seriousness of the AE.

SERIOUSNESS

An SAE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization, is a congenital abnormality (offspring of subject), or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition).

Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (eg, hospitalization for a routine right heart catheterization).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (eg, pre-planned operation which does not lead to further complications, etc).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

An estimate of causality between a specified AE and the study drug is made by the Investigator. Several factors should be considered when determining causality. These factors include temporal relationship and response to withdrawal or reintroduction of the study drug.

Definitions of the causality categories are as follows:

- NOT RELATED – There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE, or any of the following:
  - An event that precedes the first administration of study drug
  - An event for which the cause is clearly related to an external event
  - Temporal relationship to study drug is atypical
  - Is readily explained by an intercurrent illness AND has an expected level of severity, duration, and resolution
  - An alternative explanation (concomitant drug, intercurrent illness) is likely
- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:

- Has a reasonable temporal relationship to study drug
- The event has a plausible biological link to the activity of the study drug
- Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration, or complication

- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge—the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
  - Has a reasonable temporal relationship to study drug
  - The event has a plausible biologic link to the activity of the study drug
  - Not readily explained by an intercurrent illness
  - Not readily explained by external event
  - Improves on discontinuation of study drug
  - If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose or regimen of the study drug was not changed.
- Dose Increased – The dose or regimen of study drug was increased.
- Dose Decreased – The dose or regimen of study drug was decreased.
- Drug Interrupted – Administration of the study drug was stopped temporarily.
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted.
- Unknown – Changes to the administration of the study drug cannot be determined.
- Not Applicable

NOTE: Only the last study drug action should be recorded in the eCRF. For example, if the study drug is withdrawn and then the decision is made to restart, the dose modification of "Drug interrupted" should be reported on the SAE form.

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.
- Recovered/Resolved with Sequelae – The AE is considered resolved; however, there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to

be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.

- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the AE cannot be determined.