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

Protocol TDE-PH-310

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects with Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy" Amendment 8 dated 09 August 2017, and agree to abide by all provisions set forth therein.

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

I also have read the current Clinical Investigator's Brochure for UT-15C (treprostinil diethanolamine) and acknowledge that review of the information contained in the Clinical Investigator's Brochure is a requirement for Investigators before using UT-15C (treprostinil diethanolamine) in a clinical trial.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and ethics approval documents have been obtained.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

LIST OF ABBREVIATIONS

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
CI	Cardiac Index
C_{max}	Maximum Concentration
CO	Cardiac Output
CO_2	Carbon Dioxide
CTD	Connective Tissue Disease
CTM	Clinical Trial Material
CYP	Cytochrome P450
DMC	Data Monitoring Committee
dL	Deciliters
eCRF	Electronic Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEA	European Economic Area
ERA	Endothelin Receptor Antagonist
FEV_1	Forced Expiratory Volume at One Second
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
Hg	Mercury
HIV	Human Immunodeficiency Virus
H-L	Hodges-Lehmann
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional/Independent Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

LFTs	Liver Function Tests
μmol	Micromols
NTP	National Toxicology Program
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PAPd	Diastolic Pulmonary Artery Pressure
PAPm	Mean Pulmonary Artery Pressure
PAPs	Systolic Pulmonary Artery Pressure
PCWPm	Mean Pulmonary Capillary Wedge Pressure
PDE5-I	Phosphodiesterase-5 Inhibitor
PGI_2	Prostacyclin
PFO	Patent Foramen Ovale
PhRMA	Pharmaceutical Manufacturers Association
PT	Prothrombin Time
PVR	Pulmonary Vascular Resistance
RAPm	Mean Right Atrial Pressure
RHC	Right Heart Catheterization
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
SAPd	Diastolic Systemic Arterial Pressure
SAPm	Mean Systemic Arterial Pressure
SAPs	Systolic Systemic Arterial Pressure
SAS	Statistical Analysis System
sGC	Soluble Guanylate Cyclase
SvO_2	Mixed Venous Oxygen Saturation
T4	Thyroxine
TID	Three Times Daily
TLC	Total Lung Capacity
TSH	Thyroid Stimulating Hormone
UT-15C	Treprostinil Diethanolamine (also known as treprostinil diolamine)
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

PROTOCOL SYNOPSIS

Title	A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects with Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy
Study Phase	III
Indication	Pulmonary Arterial Hypertension (PAH)
Primary Objective	To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared to placebo with PAH-approved oral monotherapy on time to first adjudicated clinical worsening (morbidity or mortality) event, as defined by at least one of the events listed below: • Death (all causes) • Hospitalization due to worsening PAH defined as: o Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or o Lung or heart/lung transplantation; or o Atrial septostomy • Initiation of an inhaled or infused prostacyclin (PGI_2) for the treatment of worsening PAH • Disease progression (all criteria required): o A decrease in six minute walk distance (6MWD) of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by 2 six-minute walk tests (6MWT) performed on different days o Worsening of PAH symptoms, which must include either: ▪ An increase in functional class from Baseline *or* ▪ Appearance or worsening of symptoms of right heart failure since Baseline • Unsatisfactory long-term clinical response (all criteria required) o Randomized to receive study drug for at least 24 weeks

	○ A decrease from Baseline in 6MWD at Week 24 and beyond at two consecutive visits on different days ○ Sustained WHO Functional Class III or IV symptoms for at least 24 weeks consecutively
Secondary Objectives	To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared to placebo with PAH-approved oral monotherapy on the following: • Exercise capacity as assessed by 6MWD measured at Week 24 • Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 24 • Combined 6MWD/Borg dyspnea score at Week 24 • Exercise capacity as assessed by 6MWD measured at each visit up to Week 48 other than Week 24 • Borg dyspnea score • World Health Organization (WHO) Functional Class • Right heart catheterization (RHC) hemodynamics at Week 24 (optional) • Safety (vital signs, adverse events [AEs], clinical laboratory parameters, electrocardiograms)
Exploratory Objectives	• Optional evaluation of biomarkers • Optional evaluation of pharmacogenomics
Study Design	International, multi-center, randomized, double-blind, placebo-controlled, clinical worsening study in subjects with PAH receiving background oral monotherapy.
Sample Size	At least 610 subjects with a maximum of 850 subjects will be enrolled and randomly allocated (1:1) to receive either UT-15C or placebo.
Summary of Subject Eligibility Criteria	Eligible subjects must be 18 to 75 years of age (inclusive) at the time of signing informed consent, have a diagnosis of idiopathic or heritable PAH, PAH associated with connective tissue disease (CTD), PAH associated with repaired congenital systemic-to-pulmonary shunt (at least one year since repair), PAH associated with human immunodeficiency virus (HIV) infection, PAH associated with appetite suppressant or toxin use. Eligible subjects may not have received a PGI_2 (except if used during acute vasoreactivity testing) within 30 days before randomization. Subjects must be receiving only one PAH-approved oral therapy for at least 30 days prior to randomization and at a stable dose for a minimum of 10 days prior to randomization. The Baseline 6MWD must be at least 150 meters.

Drug Dosage and Formulation	**Background Regimen**: Every subject must have been receiving background monotherapy with one PAH-approved oral therapy for at least 30 days at randomization, and must have been receiving a stable dose for a minimum of 10 days at randomization. Once randomized, subjects must remain on the same dose of background oral PAH monotherapy for the duration of the study. In the event a subject must discontinue their background PAH oral therapy for any reason (e.g. AE), they must be switched to another agent within the same class of medication, if available and clinically appropriate per the Investigator's discretion. If no alternative therapy in the same class of medication is available and appropriate, the subject should be switched to a different class of approved oral PAH therapy. The minimum dose of oral PAH therapy used during the study must comply with the approved prescribing information for the product. **Experimental Regimen**: All subjects will receive oral treprostinil (UT-15C) sustained release tablets or matching placebo. Study drug may be provided in 0.125, 0.25, 0.5, 1, and 2.5 mg sustained-release tablets to be administered three times (TID) daily. The first dose of study drug (0.125 mg) should be taken by the subject at the study site within 10 minutes of consuming food. Oral dosing of study drug will then continue at 0.125 mg TID (every 6 to 8 hours) with food. Dose escalations can occur no more than every 24 hours (three consecutive doses) in 0.125 mg increments TID during the first four weeks of the study. Following 4 weeks of treatment, dose escalation may occur no more than every 24 hours in either 0.125 mg or 0.25 mg increments TID. The maximum dose allowed will be 12 mg TID. Note that sudden dose escalations or reductions may lead to intolerable adverse effects or worsening of PAH, respectively, and gradual dose titrations are recommended to reduce the risk to subjects. Placebo will be identical in size, shape, and color to the respective active tablets.
Control Group	Placebo with PAH-approved oral monotherapy
Route of Administration	Oral

Procedures	*Study Visit Schedule*: Subjects will be assessed during Screening and Baseline visits to determine eligibility for the study. Once randomized, subjects will return for visits every 4 weeks for the first 12 weeks, then every 12 weeks for the duration of the study. Subjects will continue in the study until they meet the definition of clinical worsening or approximately 205 adjudicated clinical worsening events have occurred. If a subject clinically worsens during the study and receives short-term (28 days or less) treatment with parenteral or inhaled PGI_2 therapy for treatment of PAH, they will be permitted to enter the open-label extension study (TDE-PH-311). If a subject discontinues the study for any reason other than clinical worsening, they will not be permitted to enter the open-label extension study. Otherwise, all subjects participating in the study will have the opportunity to transition to the open-label study once approximately 205 adjudicated clinical worsening events have occurred. The following efficacy and safety assessments will occur during the course of the study: *Efficacy Assessments*: Clinical worsening, exercise capacity (6MWD and Borg dyspnea score) measured within 3 to 6 hours following the last dose of study drug, WHO Functional Class, and NT-proBNP. Optional assessments include hemodynamics, biomarkers, and pharmacogenomics. *Safety Assessments*: AE reports, vital signs, clinical laboratory parameters, electrocardiograms (ECG).

Statistical Considerations	Approximately 205 adjudicated clinical worsening events will provide at least 90% power with a Type I error rate of 0.05 (two-sided hypothesis) to detect a difference in the time to clinical worsening between treatment groups, assuming exponential distributions and an underlying hazard ratio of 0.62. Assuming a placebo median event time of 32 months (which corresponds to an event rate of 23% at Month 12), this hazard ratio corresponds to a median time to event of 51 months for the UT-15C group, or an event rate of 15% at Month 12. If accrual of subjects is completed during the first three years and 10% of the subjects drop out by the end of the study, a total sample size of at least 610 subjects with a maximum of 850 subjects is expected to generate approximately 205 adjudicated events over the course of the study. The primary efficacy endpoint will be tested at an interim analysis when 75% of total adjudicated events have occurred with an alpha spending of 0.020 and at the final analysis at an alpha of 0.044 with the overall Type I error rate at 0.05. Efficacy boundaries for early stopping of the trial for efficacy is calculated based on O'Brien-Fleming alpha-spending function.
Sponsor	United Therapeutics Corporation 55 TW Alexander Dr. Research Triangle Park, NC 27709 USA

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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 common to 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.

The typical etiologies of PAH include idiopathic, heritable or associated with collagen vascular/connective tissue disease, portal hypertension, infection with the human immunodeficiency virus (HIV), history of cocaine inhalation and exposure to appetite suppressant drugs. An estimated annual incidence of approximately 2 cases per million has been reported for idiopathic PAH [Rich, 1987; Rubin 1997].

There are three 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 a number of 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 include: (1) intravenous PGI_2 (epoprostenol sodium or Flolan®, Veletri®); (2) the PGI_2 analogues subcutaneous (SC), intravenous (IV), and inhaled treprostinil (Remodulin®, Tyvaso®), oral treprostinil diethanolamine (also referred to as treprostinil diolamine; Orenitram®), oral selexipag (Uptravi®), and inhaled iloprost (Ventavis®); (3) the phosphodiesterase-5 inhibitors (PDE5-I), tadalafil (Adcirca®) and sildenafil (Revatio®); (4) the oral endothelin receptor antagonists (ERA), bosentan (Tracleer®), ambrisentan (Letairis®, Volibris®), and macitentan (Opsumit®), and (5) a soluble guanylate cyclase (sGC) stimulator, riociguat (Adempas®).

Approval of current PAH-specific pharmacotherapies has traditionally been based upon the 6MWT. The 6MWT is an assessment of exercise capacity and remains a standard measure of

efficacy for trials of investigational medicines in subjects with PAH. However, recent literature has questioned the clinical relevance, variability, and sensitivity of the 6MWT as a primary endpoint to assess the efficacy of treatments for PAH. Although the 6MWT is still viewed as a valuable tool for measuring clinical efficacy of PAH therapies, a composite endpoint of 'time to clinical worsening' is emerging as an alternative endpoint that allows for assessment of long-term efficacy of investigational drugs for PAH [McLaughlin, 2009].

1.2 TREPROSTINIL DIETHANOLAMINE BACKGROUND

1.2.1 General Pharmacology

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 SC, 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 (ADP) 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, 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.

Treprostinil diethanolamine (UT-15C) was selected from a series of treprostinil salts based on critical physicochemical characteristics (e.g., solubility, hygroscopicity, melting point) with a

goal of delivering treprostinil by the oral route as a sustained release (SR) dosage form. In solution, both treprostinil sodium and treprostinil diethanolamine are disassociated from their respective salt counter-ions and exist as the freely ionized form of treprostinil. As a result, the bioactive form present in the bloodstream is identical irrespective of the selection of the counter-ion.

A rat blood pressure model study confirmed that the diethanolamine salt of treprostinil exhibits dose dependent pharmacological activity with a cardiovascular profile comparable to that of treprostinil. Overall, no highly active metabolite has been identified, as all the metabolites evaluated had greatly reduced activity compared to UT-15C. Thus, it would appear that the observed pharmacological profile of UT-15C reflects the activity of the parent molecule, treprostinil, and that the contribution to that profile of any known metabolite that would be formed in vivo would be minimal.

1.2.2 General Toxicology

UT-15C is a novel salt form of Remodulin® (treprostinil) Injection and Tyvaso® (treprostinil) Inhalation Solution, which are approved in the United States and other countries for the treatment of patients with PAH. The active pharmaceutical ingredient, treprostinil, exists as the sodium salt in the drug product of Remodulin and Tyvaso. Given that the only change to the drug substance synthesis route for UT-15C is the diethanolamine addition step, and treprostinil is not altered, the bioactive form of treprostinil diethanolamine and treprostinil sodium is predicted to be identical. Therefore, in addition to the nonclinical studies conducted with UT-15C, an extensive amount of pharmacology, pharmacokinetic, and toxicology information on treprostinil sodium is available from Remodulin and Tyvaso development.

During the development of Remodulin, treprostinil sodium was administered SC and/or IV in acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies, and has a well-defined clinical safety profile. Treprostinil sodium was administered via continuous infusion to both rats and dogs in toxicity studies for up to 6 months, which supported the chronic administration of Remodulin to patients.

In addition to the extensive toxicology data with treprostinil sodium, the toxicity and toxicokinetic profiles of UT-15C have been evaluated in acute and repeat dose oral toxicity studies of up to 13 weeks in duration in rodents and up to 9 months duration in dogs. UT-15C has also been evaluated in reproductive-developmental toxicity studies in pregnant rats and rabbits and in an in vivo rat micronucleus assay.

Nonclinical findings from 13 week toxicology studies with UT-15C have included dose dependent, yet transient decreases in mean body weight gain and food consumption in both rats and dogs and soft/mucoid stools, diarrhea, and vomitus in dogs. Many of these findings have been seen previously during development of Remodulin and are consistent with PGI_2-induced effects. In addition, post-mortem findings in rats administered UT-15C included changes in organ weight data and histological findings related to the adrenal gland, heart, spleen, thymus and bone marrow; some of which were not seen with Remodulin. The majority of these findings were reversible following a 4-week recovery period. Data from a 9-month dog study provides additional toxicology information following chronic dosing. UT-15C was reasonably well-tolerated following daily oral administration at dose levels up to 35 mg/dog/day for 9 months. The primary adverse effect was judged to be gastrointestinal disturbance, evidenced by increased incidence of soft stools, mucoid stools and diarrhea. By the end of the study, all dogs were in good condition. No systemic adverse effects were detected as judged by ophthalmology, ECG, clinical pathology and histopathological examination.

In vitro genotoxicity studies with UT-15C have not been conducted; however, data are available for such studies using high doses of Remodulin (treprostinil sodium). Remodulin (treprostinil sodium) was non-mutagenic in bacterial reverse mutation assays (Ames assay) at concentrations up to 5000 mcg/plate with and without S9 metabolic activation, and in the mouse lymphoma assay at concentrations up to 400 mcg/mL without S9 metabolic activation and up to 300 mcg/mL in the presence of S9.

UT-15C was tested in vivo in the rat micronucleus assay, which aimed to evaluate the potential of UT-15C to increase the incidence of micronucleated polychromatic erythrocytes in bone marrow of rats. The results of the assay indicated that oral administration of UT-15C

at total doses up to and including a dose of 50 mg treprostinil (equivalent to 63.4 mg UT-15C/kg) did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in either male or female SD rats. Mortality observed at the high dose indicates systemic exposure of animals to the test article. Based upon these findings, treprostinil diethanolamine (UT-15C) was concluded to be negative in the rat micronucleus assay.

Segment I (rat) and Segment II (rat and rabbit) reproductive and developmental toxicology studies have also been conducted. No adverse effects for fetal viability/growth and fetal development (teratogenicity) were seen in rats at or below 20 mg/kg/day or rabbits at or below 0.5 mg/kg/day. At high doses, there were teratogenic effects of UT-15C observed when administered to rabbits. Findings included increased fetal incidence of external, soft tissue, and skeletal malformations. Additionally, a Segment III reproductive and developmental toxicology study has been conducted in female rats. F0 female rats receiving 10 mg/kg/day had decreased food consumption and body weights during gestation, increased duration of gestation, had slight decreases in the viability and number of pups per litter, and pups with decreased mean neonatal body weights. F1 pups of females that received 20 mg/kg/day had abnormalities in physical development (developmental landmarks), reflex development, exploratory behavior, learning and memory, and sexual maturation.

A six month carcinogenicity study in hemizygous Tg.rasH2 mice administered UT-15C at daily oral doses of 3, 7.5, 15 mg/kg and 5, 10, 20 mg/kg in females and males, respectively, for 26 weeks did not increase the incidence of neoplastic lesions. A two year rat carcinogenicity study is ongoing.

Studies have been conducted by the United States National Toxicology Program (NTP) to determine whether diethanolamine by itself (without treprostinil or any other drug) causes cancer. Two years of topical administration of diethanolamine to mice produced an increased incidence (compared to a control group) of malignant liver tumors in males and females, as well as an increased incidence of malignant kidney tumors in males. Doses used in this study were approximately 720 to 2900 times higher (based on mg/m^2 dosing) than the proposed starting doses for the UT-15C clinical studies. However, in transgenic mice and rats, topical

administration of diethanolamine for twenty weeks and two years, respectively, was not associated with the development of any cancers. The relevance of the mouse tumor findings to humans is currently unknown. Diethanolamine is listed on the FDA database of inactive ingredients for a number of approved drug products with no apparent safety concerns.

A Good Laboratory Practices (GLP) cardiovascular safety pharmacology study (Study 1259DU16.003) to evaluate diethanolamine effects, independent of treprostinil, on cardiovascular function in telemetered dogs was conducted. Since there are 0.269 grams of diethanolamine per each gram of treprostinil in UT-15C, for this study, doses of diethanolamine were selected that were similar or higher than the amount of diethanolamine contained in the doses of UT-15C assessed in the UT-15C cardiovascular safety pharmacology study (Study 1259DU16.002). Doses of 0, 2, 3, and 4 mg/kg/day of diethanolamine (equivalent to the amount of diethanolamine administered with 7, 11, and 15 mg/kg/day of treprostinil, the free acid of UT-15C), were selected to be administered to each of one group of four telemetered male dogs. Data support that oral administration of diethanolamine at doses up to 2 mg/kg/dose twice daily (BID; 4 mg/kg/day) to male beagle dogs was not associated with any definitive changes in arterial pressure, heart rate or electrocardiogram parameters. In addition, no abnormal clinical signs were noted in the animals dosed with the vehicle or with any of the doses of diethanolamine.

1.2.3 Clinical Pharmacology

In solution, both treprostinil sodium and treprostinil diethanolamine are disassociated from their respective salt counter-ions and exist as the freely ionized form of treprostinil. As a result, the bioactive form present in the bloodstream is identical irrespective of the selection of the counter-ion. Given this premise, the development of this new diethanolamine salt of treprostinil is expected to retain the bioactivity and safety profile of treprostinil sodium.

The most frequent adverse events (AE) associated with Remodulin in clinical trials of patients with PAH were related to the pharmacological properties of Remodulin and were generally not serious. These PGI_2-related AEs included diarrhea, headache, and nausea. Remodulin has not been associated with any significant changes in laboratory parameters or end-organ toxicity. The safety profile noted in the open label extension study, with much longer

durations of exposure and a larger, more diverse patient population, was consistent with the profile noted in the controlled trials. To date, well over 7000 subjects and patients have been exposed to Remodulin. This number includes patients who have received single administration, to patients receiving continuous infusion for greater than 10 years.

UT-15C has been administered to approximately 1800 subjects in Phase 1 to 3 clinical trials. UT-15C doses of up to 3 mg BID have been administered to healthy volunteers and patients with PAH have received up to 27.5 mg three times daily (TID) in the ongoing Phase 2 to 3 development program. The average exposure is approximately two years; the longest exposure is approximately seven years.

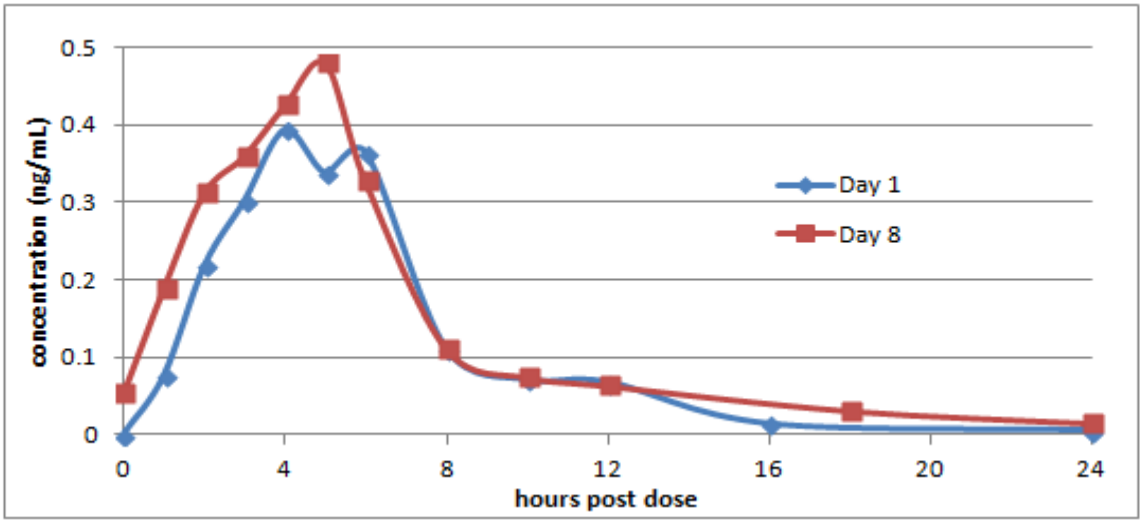
The absolute bioavailability of the UT-15C 1 mg tablet is 17% compared with IV Remodulin. Following administration, treprostinil diethanolamine is widely distributed. Treprostinil is approximately 96% protein bound with no effect on warfarin or digoxin displacement. Pharmacokinetic data (area under the curve; AUC) indicate that Day 1 pharmacokinetic data are predictive of Day 13 and linearity was observed in plasma exposure comparing 1 mg and 2 mg doses in healthy volunteers. Food, particularly a high calorie meal, has been observed to increase absorption and prolong the systemic exposure to treprostinil, contributing to the desired pharmacokinetic profile. Consistent with in vitro studies, clinical studies assessing the impact of induction and inhibition of the cytochrome P450 (CYP) 2C8 and CYP 2C9 metabolic pathways on treprostinil diethanolamine indicate that CYP 2C8 appears to be of major importance and CYP 2C9 of minor importance to in vivo metabolism of UT-15C in humans.

To date, the majority of UT-15C studies have been conducted with BID dosing. In an attempt to understand the pharmacokinetics of TID dosing a study was conducted in healthy volunteers. In this open-label, single-center study 19 healthy subjects received 0.5 mg TID for 7 days. On the morning of Day 1 subjects received a single 0.5 mg dose, on Days 2 to 7 the subjects received TID dosing of 0.5 mg (approximately 8AM, 2PM, and 8PM) with a meal. On the morning of Day 8, the subjects received a final dose of 0.5 mg.

Intensive 24 hour PK sampling occurred following the 8AM doses on Days 1, 7, and 8. Trough samples were collected prior to the morning (8 AM) and evening (8PM) doses on Days 4, 5, and 6.

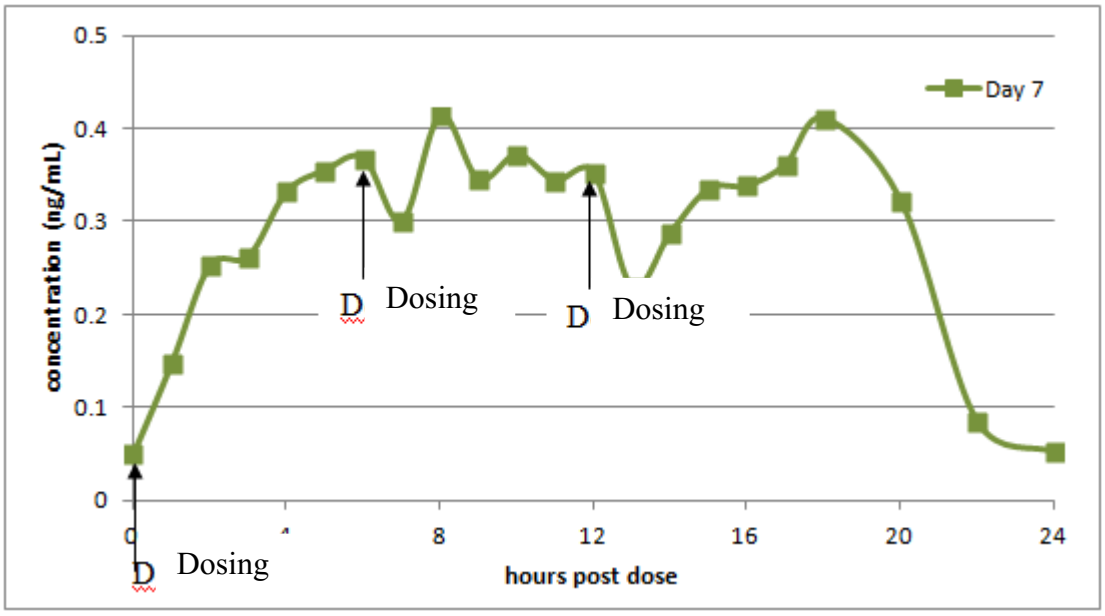
Nineteen subjects (9F: 10M) with a mean age of 35.2 years (range: 20 to 54) were enrolled. On Day 1 the mean (±SD) maximum plasma concentration (C_{max}) of treprostinil was 0.574±0.22 ng/mL, occurring at a median time of 4 hours (range: 2 to 6 hrs). In comparison, the Day 8 mean (±SD) C_{max} was 0.615±0.32 ng/mL, occurring at a median time of 4 hours (range: 1 to 6 hrs) (Figure 1-1).

Figure 1-1 Mean Plasma Treprostinil Concentration vs Time Curve Following the First Single 0.5 mg Dose of UT-15C on Day 1 and Following the Last Dose of 0.5 mg on Day 8 at Steady State



On Day 7, the mean C_{max} (±SD) was 0.810±0.491 ng/mL, occurring at a median time of 14 hours (range: 6 to 20) following the morning dose (Figure 1-2). This indicates that maximum concentration during a daily interval at steady state occurs after the evening (or third) dose of the day.

Figure 1-2 Mean Steady-State Plasma Treprostinil Concentration vs Time Curve Following Administration of 0.5 mg TID of UT-15C



Mean trough plasma concentrations prior to the morning dose on Days 5, 6, 7, and 8 were 0.049, 0.049, 0.050, and 0.053 ng/mL, respectively. Mean trough concentrations prior to the evening dose on Days 4, 5, 6, and 7 were 0.487, 0.396, 0.437, and 0.353 ng/mL, respectively.

Fifteen AEs occurred in seven subjects and primarily included known PGI_2 class-effect related AEs (e.g., headache, diarrhea, and jaw pain).

A comprehensive description of UT-15C (treprostinil diethanolamine), including the pharmacology, toxicology, and clinical studies completed to date may be found in the most recent Investigator's Brochure.

1.2.4 Efficacy and Safety Data

UT-15C has previously been evaluated in three randomized, placebo-controlled Phase 3 studies (TDE-PH-301, TDE-PH-302, and TDE-PH-308). Additionally, subjects completing these studies have been provided long-term access to UT-15C in an open-label extension study (TDE-PH-304). To date, over 1000 PAH patients have been exposed to study drug (UT-15C or placebo) in the TDE-PH-301, TDE-PH-302, and TDE-PH-308 studies and over 890 patients have received UT-15C in the open-label extension study.

TDE-PH-301 was a 16-week, randomized, double-blind, placebo-controlled, international Phase 3 efficacy and safety study of treprostinil diethanolamine (UT-15C), in patients with PAH. Patients received UT-15C or placebo BID in combination with an ERA, a PDE5-I, or both. The primary endpoint was placebo-corrected change in 6MWD from Baseline to Week 16. Secondary endpoints included Borg dyspnea score, dyspnea-fatigue index, WHO Functional Class, and time to clinical worsening. Study drug dose was titrated up to a maximum of 16 mg BID based on clinical response and study drug tolerability.

Three-hundred fifty-four subjects were enrolled with 30% receiving an ERA alone, 25% a PDE5-I alone, and 45% both agents. The population was 81% female, predominantly WHO Functional Class III (76%), and had a mean baseline 6MWD of 346 m. PAH etiology included idiopathic or heritable PAH (66%), or PAH associated with CTD (26%), repaired congenital systemic-to-pulmonary shunt (7%), or HIV infection (1%). There were no remarkable demographic differences between treatment groups.

Twenty-two percent of subjects discontinued UT-15C therapy compared to 14% in the placebo group. The primary reason for discontinuation was AEs: 14% in the UT-15C group compared to 5% in placebo. There were three deaths in each of the treatment groups.

The Hodges-Lehmann (H-L) estimate of 6MWD placebo corrected median change from baseline at Week 16 was +11 m (p=0.072). The change in 6MWD was significant at Week 12 (+13 m, p=0.015). The lack of significance at Week 16 may be attributable to the number of subjects who did not provide an efficacy measure at Week 16 due to discontinuing from the study prematurely.

Secondary endpoints of the combined 6MWD and Borg dyspnea score and the dyspnea-fatigue index demonstrated statistically significant changes at Week 16 for UT-15C compared to Baseline (p=0.013 and 0.01, respectively).

TDE-PH-301 was initiated with subjects administered a 1 mg starting dose with dose increases in 1 mg increments. Additional tablet strengths of 0.5 and 0.25 mg were made available to subjects at sequentially later times in the study. A post-hoc analysis demonstrated

that during the course of the study those subjects with access to 0.25 mg tablets at randomization had a lower discontinuation rate due to AEs (0%, n=23) as well as a higher H-L estimate of 6MWD treatment effect (+28.5 m) at Week 16. Presumably titrating up the dose of study drug slowly with smaller increments may allow subjects to tolerate and thereby maintain therapy on UT-15C and achieve optimal dosing. In addition, those subjects that were able to titrate to doses between 1.25 and 3.25 mg BID and doses greater than or equal to 3.5 mg BID also demonstrated a more robust treatment effect of +18 and +34 m, respectively. Thus, premature discontinuations and inability to achieve doses greater than 1 mg BID during TDE-PH-301 appear to have muted the overall treatment effect detected by the study.

TDE-PH-302 was a 12-week, randomized (2:1 UT-15C to placebo), double-blind, placebo-controlled, international Phase 3 efficacy and safety study of UT-15C in patients with PAH not currently receiving approved background therapy. The primary endpoint was placebo corrected median change in 6MWD from Baseline to Week 12. Secondary endpoints included Borg dyspnea score, dyspnea-fatigue index, WHO Functional Class and time to clinical worsening. Study drug dose was titrated up to a maximum of 12 mg BID based on clinical response and study drug tolerability.

The study enrolled 349 subjects who were not receiving any approved PAH medication, with the population for primary analysis consisting of 228 subjects who had access to the 0.25 mg tablet strength at randomization. These subjects were administered UT-15C or placebo BID, with the doses titrated to effect over the course of the 12-week study. The majority of subjects were in WHO Functional Class II (33%) and class III (66%) of varied etiologies, including idiopathic or heritable PAH (75%), CVD associated PAH (19%), and PAH associated with HIV or other associated conditions (6%). The subjects' mean Baseline 6MWD was approximately 330 m.

The primary efficacy analysis comparing change in 6MWD from Baseline to Week 12 between treatment groups in the primary analysis population (n=228) was +23 m (p=0.0125, H-L estimate). The UT-15C group improved by a median of +25 m compared to -5 m change in the placebo group.

The combined 6MWD and Borg dyspnea score was also significantly improved (p=0.0497) at Week 12. Preliminary analysis of other secondary efficacy measures, including change in trough 6MWD at Week 11, change in dyspnea fatigue index, change in Borg dyspnea score, change in WHO Functional Class, time to clinical worsening (as defined by death, transplantation, atrial septostomy, hospitalization due to PAH or at least a 20% decrease in 6MWD and initiation of another approved PAH therapy), and PAH signs and symptoms at Week 12 did not differ significantly between the UT-15C and placebo groups (p>0.05).

An analysis of all 349 subjects enrolled in the study demonstrated that those subjects receiving UT-15C improved their median 6MWD by approximately +25.5 m (H-L estimate, p=0.0001) as compared to subjects receiving placebo.

AEs during the study included headache, nausea, diarrhea, and flushing, which were expected in subjects receiving prostanoid therapy. A low discontinuation rate due to AEs in the primary analysis population and the type of AEs resulting in discontinuation (mostly PGI_2 related, which are not life threatening) indicate that use of UT-15C may provide a significant improvement in the safety profile of treprostinil and result in a reduction in the occurrence of life-threatening AEs compared with parenteral treprostinil therapy (e.g., central venous catheter-related blood stream infection).

TDE-PH-308 was a 16-week, randomized, double-blind, placebo-controlled, international Phase 3 efficacy and safety study of UT-15C in patients with PAH. Patients received UT-15C or placebo BID in combination with either an ERA, a PDE5-I, or both. The primary endpoint was placebo-corrected change in 6MWD from Baseline to Week 16. Secondary endpoints included Borg dyspnea score, dyspnea-fatigue index, WHO Functional Class and time to clinical worsening. Study drug dose was titrated up to a maximum of 16 mg BID based on clinical response and study drug tolerability.

Three-hundred-ten subjects (157 UT-15C and 153 placebo) were randomized, received a dose of study drug, and contributed to the analysis population for the study. The study population had a mean age of 51 years (range 18 to 76 years), was 78% female and had a diagnosis of idiopathic or heritable PAH (65%), PAH related to CVD (31%), PAH related to HIV infection

(2%), or PAH related to repaired systemic-to-pulmonary shunts (1%). The population was predominantly WHO Functional Class III (73%) with a mean Baseline 6MWD of 333 m. As for PAH-approved background therapy, 53 (17%) subjects were receiving ERA therapy alone, 132 (43%) subjects were receiving a PDE5-I alone, and 125 (40%) subjects were receiving the combination of an ERA and a PDE5-I at Baseline. The UT-15C and placebo groups were well balanced across all Baseline indices.

The primary efficacy analysis comparing change in 6MWD from Baseline to Week 16 between treatment groups was +10 m (H-L estimate; p=0.089). The UT-15C group improved by a median of +15 m compared to a +11 m median change in the placebo group. Placebo-corrected changes from Baseline in 6MWD at Week 16 by PAH-approved background therapy were as follows: ERA only (H-L estimate of treatment effect = +7.7 m; p=0.739), PDE5-I only (H-L estimate = +15.0 m; p=0.054), and combination ERA and PDE5-I (H-L estimate = +4.0 m; p=0.674). The mean ± SD maximum dose of UT-15C was 3.1±1.9 mg BID in the UT-15C group as compared to 6.1±3.6 mg BID in the placebo group. Secondary endpoints including change in 6MWD at Weeks 4, 8, and 12, combined 6MWD and Borg dyspnea score, dyspnea-fatigue index, clinical worsening, serum NT-proBNP, WHO Functional Class, quality of life, and symptoms of PAH at Week 16 were not found to be statistically significant.

TDE-PH-304 is a long-term, open-label, international, Phase 3 study designed to provide access to UT-15C for subjects previously enrolled in studies TDE-PH-301, TDE-PH-302, TDE-PH-308, or other specified studies conducted during the UT-15C development program. Secondary objectives of the study are to assess the long-term safety of UT-15C in PAH patients and to assess the effect of continued therapy on exercise capacity via 6MWD following one year of treatment with UT-15C. As of 01 September 2015, over 896 subjects were enrolled, representing 2377.7 patient-years of exposure. The mean and maximum duration of exposure was 138.8 and 444.9 weeks (2.66 and 8.53 years), respectively. The mean dose of oral treprostinil achieved was 3.9, 4.5, 4.8, 5.0, 5.5, 5.9, and 5.9 mg BID at 1 year (N=605), 2 years (N=472), 3 years (N=337), 4 years (N=230), 5 years (N=119), 6 years (N=77), and 7 years (N=37), respectively. AEs were typical of PGI_2 therapy; laboratory

findings were unremarkable and did not suggest any specific safety concerns related to long-term treatment with UT-15C. Following 12 months of oral treprostinil treatment, the mean 6MWD increased by +25 meters as compared with Baseline. Kaplan-Meier analysis of subject survival demonstrated 1-, 2-, and 3-year survival estimates of approximately 93.6%, 87.9%, and 82.2%, respectively.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN PAH

Prostacyclin is a potent endogenous vasodilator and inhibitor of platelet aggregation. A synthetic salt of PGI_2 (i.e., Flolan) has been previously shown to prolong survival in patients with PAH [Barst 1996]. However, due to its very short half-life and chemical instability, Flolan has to be continuously infused by intravenous delivery. Treprostinil sodium is a chemically stable, longer acting analogue that has shown clinical effectiveness when administered by subcutaneous, intravenous (Remodulin) [Remodulin package insert, 2013], or inhaled routes (Tyvaso) [Tyvaso package insert, 2013].

Parenteral PGI_2 are considered by many providers as the "gold standard" for treatment of PAH; however, they are typically used later in the course of the disease due to the risks and difficulties associated with administration. Consequently, physicians managing patients with PAH commonly initiate oral monotherapy, to allow patients to benefit from the simplicity of an oral dosage form.

Effective treatment of PAH often requires combination therapy with several drugs. Current guidelines suggest that if patients in WHO Functional Classes II, III, or IV do not demonstrate improvement, sequential combination therapy with several PAH-specific drugs is appropriate [Barst 2009]. Several studies have previously demonstrated a benefit of sequential combination therapy, particularly when combining PGI_2 treatment with other PAH-specific treatments. The STEP-1 study evaluated the efficacy of iloprost and bosentan combination therapy over 12 weeks, resulting in a near significant increase in 6MWD ($p=0.051$) after iloprost inhalation (McLaughlin et al., 2006). The PACES study demonstrated improvements in exercise capacity and hemodynamic parameters when sildenafil and intravenous epoprostenol were used in combination (Simonneau et al., 2008). The TRIUMPH-I study evaluated the efficacy of inhaled treprostinil (Tyvaso®) compared with placebo in patients

already receiving treatment with either bosentan or sildenafil and found a statistically significant increase in 6MWD at peak and trough treprostinil exposure ($p<0.0006$ and $p<0.01$, respectively) (McLaughlin et al., 2010). An innovative salt form, treprostinil diethanolamine, has been developed to deliver PGI_2 therapy via the oral route in a solid dosage form. Because the bioactive species is the same, treprostinil diethanolamine is expected to retain a similar safety and efficacy profile as parenteral treprostinil sodium in the convenience of an oral dosage form. It has been suggested combination therapy, particularly with a PGI_2, may prevent or delay the progression of the disease and thereby prolong the time to clinical worsening.

1.4 CLINICAL HYPOTHESIS

The hypothesis of this study is that treatment with oral UT-15C combined with PAH-approved oral monotherapy as compared with placebo with PAH-approved oral monotherapy will:

- Delay time to first clinical worsening (morbidity or mortality) event

The hypothesis for the change of dosing frequency from BID to TID is that delivering more sustained concentrations of treprostinil may allow for systemic exposure to drug that more closely resembles the approved parenteral product, Remodulin, and reduce the occurrence of PGI_2 AEs previously seen with the BID regimen. Both of these improvements may allow study subjects to titrate to a more effective UT-15C dose and thus study drug may show a clinically and statistically significant difference compared to placebo in delaying time to first clinical worsening.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is:

> To assess the effect of oral UT-15C with PAH-approved oral monotherapy compared to placebo with PAH-approved oral monotherapy on time to first adjudicated clinical worsening (morbidity or mortality) event, as defined by at least one of the events listed below:
>
> - Death (all causes)

- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or
  - Lung or heart/lung transplantation; or
  - Atrial septostomy
- Initiation of an inhaled or infused PGI_2 for the treatment of worsening PAH
- Disease progression (all criteria required):
  - A decrease in 6MWD of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by two 6MWTs performed on different days*
  - Worsening of PAH symptoms, which must include either

    An increase in functional class from Baseline *or*

    Appearance or worsening of symptoms of right heart failure since Baseline
- Unsatisfactory long-term clinical response (all criteria required)
  - Randomized to receive study drug for at least 24 weeks
  - A decrease from Baseline in 6MWD at Week 24 and beyond at two consecutive visits on different days*
  - Sustained WHO Functional Class III or IV symptoms for at least 24 weeks consecutively

*Confirmatory 6MWTs should be conducted within 30 days of the qualifying decrease in 6MWD; however, confirmatory 6MWTs occurring outside of this window will still be considered to have met the definition of clinical worsening and sent to the adjudication committee for review.

2.2 SECONDARY OBJECTIVES

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

- Exercise capacity as assessed by 6MWD measured at Week 24
- NT-proBNP at Week 24
- Combined 6MWD/Borg dyspnea score at Week 24
- Exercise capacity as assessed by 6MWD measured at each visit up to Week 48 other than Week 24
- Borg dyspnea score
- WHO Functional Class
- Right heart catheterization (RHC) hemodynamics at Week 24 (optional)

- Safety
  - Clinical laboratory parameters
  - Vital signs
  - AEs
  - ECG

2.3 EXPLORATORY OBJECTIVES

- Optional evaluation of biomarkers
- Optional evaluation of pharmacogenomics

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is an international, multi-center, randomized, double-blind, placebo-controlled, event driven study in subjects with PAH. Subjects will be assessed during the Screening period to determine eligibility for the study, which will be confirmed during the Baseline visit prior to randomization. Once randomized, subjects will return for study visits every 4 weeks for the first 12 weeks, then every 12 weeks for the duration of the study. Subjects will continue in the study until either they experience clinical worsening as defined in the protocol, approximately 205 adjudicated events have occurred, or they prematurely discontinue participation in the study for any reason other than protocol-specific clinical worsening. If a subject meets the definition of clinical worsening during the study and receives only short term (28 days or less) treatment with an infused or inhaled PGI_2 therapy for worsening PAH, they will be permitted to enter the open-label extension study (TDE-PH-311). If a subject prematurely discontinues the study for any reason other than clinical worsening, or receives long-term (29 days or more) treatment with an infused or inhaled PGI_2 therapy for worsening PAH, they will not be permitted to enter the open-label extension study. Otherwise, all subjects actively participating in the study will be allowed to transition to the open-label extension study after approximately 205 adjudicated clinical worsening events have occurred.

At each scheduled visit, subjects will undergo the following efficacy assessments: clinical worsening, exercise capacity (6MWD and Borg dyspnea score), and WHO Functional Class. Plasma samples will also be collected for measurement of NT-proBNP at Baseline, Week 12

Week 24, Continued Visit 1 and at every other Continued Visit thereafter. See Table 3-1 for the overall schedule of times and events.

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

Safety will be assessed via vital signs, AEs, and clinical laboratory parameters. Subjects will also undergo a 12-lead ECG at Screening and Week 24. At every protocol-required visit, measures of exercise capacity will occur within 3 to 6 hours following administration of the last dose of study drug.

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

Table 3-1 Overall Schedule of Times and Events

STUDY PROCEDURES	**Screen/Baseline[a]**		**Treatment[k,m]**					**End of Study[m]**
Study Timeline	Day -30 to -1	Day 1 (Baseline)	Week 4[j]	Week 8[j]	Week 12[j]	Week 24[j]	Continued Visits every 12 weeks[j]	Study Drug Termination Visit[l]
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
PAH & Medical History	X							
Vital Signs[b]	X	X	X	X	X	X	X	X
Physical Examination	X							X
Clinical Worsening Assessment			X--------	---------	---------	--------	----X	X
6MWT/Borg Dyspnea Score	X[c,d]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
WHO Functional Class for PAH		X	X	X	X	X	X	X
Clinical Laboratory Tests	X[a]	X[a]			X	X	X[e]	X
Plasma N-terminal proBNP		X			X	X	X[e]	X
Urine Pregnancy Test for WOCBP	X	X	X	X	X	X	X	X
12-lead ECG[f]	X					X		X
Right Heart Catheterization (optional)		X[g]				X[h]		
Randomization		X						
Administration of Study Drug		X[i]---------	---------	--------	--------	-------	-----X	
Weekly Telephone Contact[n]		X---------	---------	--------	-------	------X		

Monthly Telephone Contact						X------	------	------X
Drug Accountability		X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X
Adverse Events	X-----	----------	---------	--------	--------	-------	-------	X
Concomitant Medications	X-----	----------	---------	--------	--------	-------	-------	X
Serum Biomarker Sample (Optional)[o]								X[o]
Urine Biomarker Sample (Optional)[o]								X[o]
Pharmacogenomic Sample (Optional)[p]								X[p]

[a] The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to randomization. Sites should provide a completed Pre-Baseline review form to the Medical Monitor which will be reviewed, signed and returned to the site prior to randomization. Sites may conduct pre-Screening activities prior to a specific subject signing an informed consent. Pre-Screening activities may include review of the site's database to identify potential patients that may be eligible for the study.

[b] Vital signs should be conducted prior to, or at least 30 minutes following, the corresponding 6MWT. Subjects should rest for 5 minutes prior to collection of vital signs

[c] If the subject has not previously undergone a 6MWT at the study site, a practice 6MWT must be conducted during the Screening period

[d] Subject should rest for 5 minutes prior to each 6MWT. All 6MWTs following randomization must be conducted 3 to 6 hours after the last dose of study drug

[e] During the Continued Visits, laboratory samples and NT-proBNP will only be collected at the first Continued Visit and at every other Continued Visit thereafter

[f] To be conducted following a minimum of 5 minutes rest in the semi-recumbent position

[g] To be conducted within 5 days prior to Randomization (inclusive) and following a minimum of 10 days on stable background PAH oral monotherapy

[h] To be conducted within 72 hours after all other Week 24 assessments; as best as possible to be performed 3 to 6 hours after previous dose of study drug

[i] First dose of study drug will be administered in the clinic following randomization; study drug dosing will continue at 0.125 mg TID (every 6 to 8 hours)

[j] The window for Week 4, 8, 12 and 24 visit assessments is ± 7 days; the window for visits following Week 24 is ±14 days.

[k] At any time during the Treatment Period, subjects may return to the study site for additional assessments as required

[l] The Study Termination Visit includes the study drug termination which should be pconducted at the time the decision is made to discontinue the study drug (prior to down titration), either because the subject has met clinical worsening criteria or is being permanently discontinued from the 310 study. The 6MWD should be conducted within 3 to 6 hours after the most recent dose of study medication and preferably before the drug is down titrated (if the subject is being permanently discontinued rather than transitioning to the TDE-PH-311 study)

[m] If subject permanently discontinues study drug before Week 24 and is ineligible for the TDE-PH-311 study, subject should be encouraged to remain in study and attend visits up to and including Week 24. The end of study assessments (survival status, AE assessment, drug accountability, concomitant medications, etc.) should be conducted after the subject has stopped taking the study medication (before or at Week 24)

[n] Weekly telephone contact should be completed and subject study drug dose must also be recorded at Week 16 and Week 20 in the eCRF. More frequent telephone calls may be necessary depending on the frequency of dose titration and to manage AEs or signs and symptoms of disease

[o] For subjects consenting to the optional biomarker samples.

[p] For subjects consenting to the optional pharmacogenomic sample.

3.2 CLINICAL ASSESSMENTS

3.2.1 Efficacy

3.2.1.1 Clinical Worsening

Clinical worsening will be assessed continuously from randomization until the subject's last study visit. All clinical worsening events will be reviewed by the sponsor Medical Monitors. To ensure subject eligibility for the open-label extension study (TDE-PH-311), subjects should remain on study drug until the clinical worsening event has been reviewed and confirmed by the Medical Monitor unless the Investigator feels it is medically necessary to discontinue study drug for the welfare of the subject. Clinical worsening (adjudicated) is defined as the occurrence of any one of the following clinical worsening (morbidity or mortality) events:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
  - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure; or
  - Lung or heart/lung transplantation; or
  - Atrial septostomy
- Initiation of an inhaled or infused PGI_2 for the treatment of worsening PAH
- Disease progression (all criteria required):
  - A decrease in 6MWD of at least 15% from Baseline (or too ill to walk) directly related to PAH progression with other co-morbidities ruled out, confirmed by two 6MWTs performed on different days*
  - Worsening of PAH symptoms, which must include either
    - An increase in functional class from Baseline *or*
    - Appearance or worsening of symptoms of right heart failure since Baseline
- Unsatisfactory long-term clinical response (all criteria required)
  - Randomized to receive study drug for at least 24 weeks
  - A decrease from Baseline in 6MWD at Week 24 and beyond at two consecutive visits on different days*
  - Sustained WHO Functional Class III or IV symptoms for at least 24 weeks consecutively

*Confirmatory 6MWTs should be conducted within 30 days of the qualifying decrease in 6MWD; however, confirmatory 6MWTs occurring outside of this window will still be considered to have met the definition of clinical worsening and sent to the adjudication committee for review.

Once a clinical worsening event occurs, it must be entered on the specified form in the electronic case report form (eCRF) and should be submitted within 48 hours after the event becomes known to the Investigator or designee. When the form is submitted, the sponsor Medical Monitor will review the event and correspond with the Investigator and site, as appropriate. Although subjects may be discontinued from the study for medical necessity at any time, subjects should not be discontinued for a clinical worsening event until the event has been reviewed by the Medical Monitor. Once the clinical worsening event has occurred, the subject will then complete the Study Drug Termination visit assessments.

Clinical worsening events that meet the definition of a serious adverse event (SAE) will follow the same reporting requirements as all SAEs (Section 9.3). These events must also be entered on the specified form in the eCRF.

In addition to the Medical Monitor reviewing all clinical worsening events as and when they occur, an independent adjudication committee will review all clinical worsening events periodically throughout the study (Section 10.8).

3.2.1.2 Six-Minute Walk Test

The intent of the 6MWT is to evaluate exercise capacity associated with carrying out activities of daily living. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements as described in Section 15.1. Prior to the start of each 6MWT the subject should rest (seated) for at least 5 minutes.

3.2.1.2.1 Practice Six Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course intended for use during the study. If no previous 6MWT has been performed at the study site, a practice 6MWT must be conducted at least 1 day prior to the Randomization 6MWT for applicable subjects.

3.2.1.2.2 Baseline Six Minute Walk Test

A Baseline 6MWT must be performed prior to initiation of study drug and should be conducted on the day of randomization. The Baseline 6MWT must be conducted no earlier than 1 day following the practice 6MWT, for applicable subjects. Once the Baseline 6MWT has been

conducted, the site will enter the subject's six-minute walk distance into an interactive voice or web response system (IVRS/IWRS). IVRS/IWRS will confirm to site personnel the subject's eligibility to participate in the study based on 6MWD, and if eligible, randomize the subject into a treatment group and allocate appropriate study drug.

3.2.1.2.3 Treatment Six-Minute Walk Tests

6MWTs will be conducted at Weeks 4, 8, 12, 24, and every 12 weeks thereafter. The 6MWT should be conducted 3 to 6 hours following the last dose of study medication. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate and mode of oxygen therapy at all subsequent 6MWT assessments; any changes in oxygen therapy administration should be noted in the eCRF. In addition, subjects receiving pulmonary rehabilitation prior to study entry should continue on the same schedule up to and including Week 24. Following Week 24, pulmonary rehabilitation may be adjusted per standard of care. Pulmonary rehabilitation may not be added to a subject's regimen between randomization and Week 24. Documentation of pulmonary rehabilitation should occur in the special circumstances section of the eCRF. Additional 6MWTs may be conducted as appropriate throughout the course of the study for the purposes of evaluating clinical worsening status.

Each 6MWT conducted after Randomization should be documented and compared to the subject's Baseline 6MWD. If a subject has a decrease of 15% or more in walk distance compared to Baseline, a second confirmatory 6MWT should be performed on a different day to assess for clinical worsening (confirmatory 6MWTs should be conducted within 30 days of the qualifying decrease in 6MWD; however, confirmatory 6MWTs occurring outside of this window will still be considered to have met the definition of clinical worsening and sent to the adjudication committee for review). If the second 6MWT also shows at least 15% decrease in 6MWD as compared to Baseline and the subject has either worsened in WHO Functional Class compared to Baseline or has the appearance or worsening of symptoms of right heart failure since Baseline, the subject will meet the 'disease progression' definition of clinical worsening and should follow steps as outlined in Section 3.2.1.1. Prior to exiting the study, the Study Drug Termination visit assessments should be conducted at the time the decision is made to discontinue study drug (prior to down titration). For subjects who meet the definition of clinical

worsening for disease progression due to at least a 15% decrease in 6MWD from Baseline, the date of the clinical worsening event will be the date of the second confirmatory 6MWT.

After the first 24 weeks of study participation, if a subject has any two consecutive 6MWTs on different days that demonstrate any decrease in 6MWD from Baseline accompanied with sustained WHO Functional Class III or IV symptoms for at least 24 weeks, consecutively, the subject will meet the clinical worsening definition of unsatisfactory long-term clinical response and should follow steps outlined in Section 3.2.1.1.

Details regarding the conduct of the 6MWT are described in Section 15.1.

3.2.1.3 Borg Dyspnea Score

The Borg dyspnea score will be assessed following each 6MWT. The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT (Section 15.1). Scores range from 0 (for the best condition) to 10 (for the worst condition).

3.2.1.4 WHO Functional Classification

The WHO functional classification for PAH (Section 15.2) will be assessed at Baseline prior to starting study drug and at all subsequent scheduled study visits, and every time the 6MWT is performed for purposes of assessing clinical worsening status.

3.2.1.5 N-terminal pro-BNP

Plasma NT-proBNP concentration is a useful biomarker for PAH as it is associated with changes in right heart morphology and function [Fijalkowska 2006]. NT-proBNP sample collection will occur at Baseline (prior to starting study drug), Week 12, Week 24, the first Continued Visit, and every other Continued Visit thereafter (i.e., Continued Visits #3, #5, #7, etc.). NT-proBNP will also be assessed at the Study Drug Termination visit.

3.2.1.6 Right Heart Catheterization (Optional Assessment)

This section describes the optional RHC assessments that may be conducted at Baseline and Week 24.

If a subject agrees to participate in the optional hemodynamic assessments, a RHC must be performed within 5 days before randomization (inclusive). The subject must be on stable

background therapy for a minimum of 10 days prior to this RHC. If a RHC is performed on the day of randomization, all other study-related assessments, other than initiation of study drug, should be performed prior to conduct of the RHC. A follow-up RHC must be performed within 72 hours following completion of Week 24 assessments. As best as possible, follow-up RHC should be performed within 3 to 6 hours of previous dose. Hemodynamic parameters to be assessed and recorded include heart rate (HR), systolic systemic arterial pressure (SAPs), diastolic systemic arterial pressure (SAPd), mean systemic arterial pressure (SAPm), systolic pulmonary artery pressure (PAPs), diastolic pulmonary artery pressure (PAPd), mean pulmonary artery pressure (PAPm), mean right atrial pressure (RAPm), mean pulmonary capillary wedge pressure (PCWPm), cardiac output (CO), arterial oxygen saturation (SaO_2), and mixed venous oxygen saturation (SvO_2). Additional hemodynamic parameters may also be calculated based on these measurements (e.g., pulmonary vascular resistance [PVR] and cardiac index [CI]). Weight and height will be collected to calculate body surface area (BSA) and index the cardiac output.

While this section describes the optional RHC assessments at Baseline and Week 24, all subjects eligible to participate in this study must either have data available from a historical RHC conducted within three years prior to the start of screening (i.e., date of signing the Informed Consent Form [ICF]), or undergo a RHC during the screening period prior to randomization with results consistent with the diagnosis of PAH as described in Section 4.1.

3.2.1.7 Optional Biomarker

For subjects consenting to the optional biomarker samples, blood and urine will be collected at the End of Study Visit for the evaluation of biomarkers. These samples will be shipped to the central laboratory for processing and storage prior to analysis. Subjects who do not wish to participate in the optional biomarker research may still participate in the clinical study.

3.2.1.8 Optional Pharmacogenomic

For subjects consenting to pharmacogenomic analysis, blood samples will be collected at the End of Study Visit for pharmacogenomics analyses. These samples will be shipped to the central laboratory for processing and storage prior to analysis. Genetic variants and/or gene expression patterns will be analyzed to evaluate their association with observed clinical response and

tolerability to prostacyclin therapy. Subjects who do not wish to participate in the optional pharmacogenomic research may still participate in the clinical study.

3.2.2 Safety

3.2.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PAH history, and physical examination will be conducted during the Screening period. 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 noted in the eCRF. Any significant changes to the subject's medical condition, physical examination, and concomitant medications must be documented throughout the course of the study. A complete physical examination will be conducted at the Study Drug Termination Visit.

3.2.2.2 Clinical Laboratory Tests

Clinical laboratory tests will be assessed at the Screening and Baseline visits prior to starting study drug. Screening and Baseline clinical laboratory assessments can be combined into a single blood draw if all eligibility criteria are met within 48 hours prior to randomization. Central laboratory data are ultimately used to qualify patients for the study. However, for patients who are well known to the Investigator and who are clinically stable, the Investigator may choose not to delay randomization while waiting for central laboratory confirmation of local laboratory values. Clinical laboratory assessments will also be assessed at Weeks 12 and 24, at the first Continued Visit, and every other Continued Visit thereafter (i.e., Continued Visits #3, #5, #7, etc.) as displayed in Appendix 15.3. Clinical laboratory tests will also be assessed at the Study Drug Termination visit.

A urine pregnancy test will be collected at Screening, Baseline, Weeks 4, 8, 12, 24, every 12 weeks thereafter, and at the Study Drug Termination Visit for women of child bearing potential (WOCBP). Screening and Baseline urine pregnancy tests can be combined into a single test if all eligibility criteria are met within 48 hours prior to randomization.

3.2.2.3 Vital Signs

Vital signs will be assessed at Screening and Baseline prior to starting study medication and at Weeks 4, 8, 12, and 24. After Week 24, vital signs will be assessed every 12 weeks and at the Study Drug Termination Visit. All vital signs will be collected prior to or at least 30 minutes following the corresponding 6MWT. Vital signs include blood pressure, peripheral (radial/brachial artery) heart rate, respiration rate, and weight. Height will be collected at the Baseline visit. Vital signs must be collected following at least 5 minutes of rest (or at least 30 minutes after a 6MWT) to ensure accurate measurement.

3.2.2.4 Adverse Events

AEs will be captured from the time the ICF is signed. 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 up to 30 days if the AE extends beyond the final visit. All 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 visit. Sections 9 and 15.4 provide the guidelines and definitions for recording AEs.

Symptoms of PAH (disease related events) should only be recorded as an AE if the event is either serious, new, or unusual with respect to intensity, frequency, duration as compared to symptoms in the subject's medical history; or there is a reasonable possibility that the event was caused by the study drug.

3.2.2.5 12-Lead ECG

Twelve-lead ECGs will be recorded after at least 5 minutes rest in the semi-recumbent position at Screening, Week 24, and at the Study Drug Termination Visit. Recordings should include lead II as a rhythm strip and contain at least five QRS complexes. ECG parameters collected include heart rate, PR interval, QT interval, QRS duration, and any clinically significant abnormalities.

3.3 NUMBER OF CENTERS

The study is an international multi-center study with approximately 150 centers participating.

3.4 NUMBER OF SUBJECTS

At least 610 subjects with a maximum of 850 subjects will be randomized (1:1 UT-15C: placebo) across all sites participating in the study in order to obtain the required number of adjudicated clinical worsening (morbidity and mortality) events.

3.5 ESTIMATED STUDY DURATION

Subjects will remain in the study until they either experience a clinical worsening event, discontinue the study for any other reason, or approximately 205 adjudicated clinical worsening events have occurred. It is estimated that the overall study duration will last for 4 years; however, this is dependent on the rate of clinical worsening events.

Subjects that discontinue and do not roll into the open-label extension study (TDE-PH-311) will be contacted approximately 30 days (±5 days) after study drug discontinuation to confirm their survival status. Subjects that complete TDE-PH-310 and roll in to the open-label extension study will also be contacted approximately 30 days (±5 days) after study drug discontinuation in study TDE-PH-310 to confirm their survival status.

Subjects may also continue to be contacted after the final study visit to assess ongoing AEs/SAEs (see Section 9.2 for additional details).

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during the Screening period and reconfirmed at the Baseline visit prior to randomization. If necessary, certain procedures may be conducted during the Screening period after obtaining informed consent to determine subject eligibility for the study.

4.1 INCLUSION CRITERIA

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

1. The subject voluntarily gives informed consent to participate in the study.
2. The subject is 18 to 75 years of age (inclusive) at Screening (i.e., date of providing written informed consent).
3. Women of child bearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as

amenorrhea for at least 12 consecutive months). Women of childbearing potential must practice true abstinence from intercourse when it is in line with their preferred and usual lifestyle, or use two different forms of highly effective contraception for the duration of the study, and for at least 30 days after discontinuing study medication. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device (IUD), or (4) partner vasectomy. For women of childbearing potential, a negative urine pregnancy test is required at Screening and Baseline prior to initiating study medication.

4. The subject, if male, must use a condom during the length of the study, and for at least 48 hours after discontinuing study medication.
5. The subject has a diagnosis of symptomatic idiopathic or heritable PAH, PAH associated with CTD, PAH associated with HIV infection, PAH associated with repaired congenital systemic-to-pulmonary shunt (at least 1 year since repair with respect to the date of providing informed consent) or PAH associated with appetite suppressant or toxin use.
6. The subject, if known positive for HIV infection, has a CD4 lymphocyte count of at least 200 cells/mm^3 assessed at Screening and is receiving current standard of care anti-retroviral or other effective medication for treatment of HIV infection.
7. The subject must have a Baseline 6MWD greater than or equal to 150 meters, in the absence of a concurrent injury, illness (other than PAH or a PAH related condition), or other confounding factor including, but not limited to, use of an aid for ambulation (e.g., use of a cane or walker) or connection to a non-portable machine, that would prevent the accurate assessment of the subject's exercise capacity.
8. The subject must be optimally treated with conventional pulmonary hypertension therapy (e.g., oral vasodilators, oxygen, digoxin, diuretics, anticoagulants as deemed appropriate by the Investigator) with no additions, discontinuations, or dose changes for a minimum of 10 days prior to randomization. The exceptions are the discontinuation or dose changes of anticoagulants and/or dose change of diuretics.
9. The subject must have been receiving a PAH-approved oral monotherapy at a minimum dose that complies with the approved prescribing information for the product for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization. The subject who previously received two PAH-approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or an sGC stimulator) will be eligible provided they received these medications concomitantly for less than or equal to 90 days cumulatively. The subject must have taken only one PAH-approved therapy for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization.
10. The subject has previously undergone a cardiac catheterization either within three years prior to the start of screening, or during the screening period, and the most recent assessment has documented a mean pulmonary artery pressure (PAPm) of at least 25 mmHg, a pulmonary capillary wedge pressure (PCWP) (or in the event a PCWP cannot be reliably obtained, a left ventricular end diastolic pressure [LVEDP]) less than or equal to 15 mmHg, and absence of unrepaired congenital heart disease (other than patent foramen ovale [PFO]). In the event that a reliable PCWP or LVEDP are unable to

be obtained during cardiac catheterization, subjects with clinically normal left heart function and absence of clinically relevant mitral valve disease on echocardiography are eligible for enrollment.

11. The subject has undergone echocardiography with evidence of clinically normal left systolic and diastolic ventricular function and absence of any clinically significant left sided heart disease (e.g. mitral valve disease). Subjects with clinically insignificant left ventricular diastolic dysfunction due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) are eligible.
12. The subject has a previous ventilation perfusion lung scan, and/or high resolution computerized tomography scan of the chest, and/or pulmonary angiography that are consistent with the diagnosis of PAH (e.g., low probability of pulmonary embolism; absence of major perfusion defects).
13. The subject has pulmonary function tests conducted within 6 months before screening or during the Screening period to confirm the following:
    a. Total lung capacity (TLC) is at least 60% (predicted value) assessed by either whole body plethysmography or helium dilution or nitrogen washout technique
    b. Forced expiratory volume at one second (FEV_1) of at least 50% (predicted value)
14. In the opinion of the Principal Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

4.2 EXCLUSION CRITERIA

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

1. The subject is pregnant or lactating.
2. The subject has previously received UT-15C.
3. The subject has received a PGI_2, (except if used during acute vasoreactivity testing) within 30 days prior to randomization or had previous intolerance or significant lack of efficacy to any PGI_2, or PGI_2 analogue, that resulted in discontinuation or inability to titrate that therapy effectively.
4. The subject has had any background conventional therapies for PAH added, removed or dose adjusted (including but not limited to oxygen, vasodilators, diuretics, digoxin, anticoagulants) within 10 days prior to randomization. The exceptions are removal or dose adjustments of anticoagulants and/or dose adjustments of diuretics.
5. The subject has received their first dose of a PAH-approved therapy less than 30 days prior to randomization, or has had their PAH-approved oral monotherapy dose changed within 10 days prior to Randomization, or the subject discontinued any PAH-approved therapy within 30 days prior to Screening, or the subject previously received two PAH-approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or an sGC stimulator) concomitantly for more than 90 days cumulatively.
6. The subject has any disease associated with PAH other than CTD, HIV infection, repaired (for at least one year) congenital systemic-to-pulmonary shunt, PAH associated

with appetite suppressant/toxin use (e.g., portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc.) or has had an atrial septostomy.

7. The subject has a current diagnosis of uncontrolled sleep apnea as defined by their physician.
8. The subject has a history of ischemic heart disease, including a previous myocardial infarction or symptomatic coronary artery disease within 6 months prior to Screening or a history of left sided myocardial disease as evidenced by a mean PCWP (or a left ventricular end diastolic pressure [LVEDP]) greater than 15 mmHg or left ventricular ejection fraction less than 40% as assessed by either multigated angiogram (MUGA), angiography, or echocardiography.
9. The subject has uncontrolled systemic hypertension as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
10. The subject has ALT or AST levels at least greater than 3 times the upper limit of normal, clinically significant liver disease/dysfunction, or known Child-Pugh Class C hepatic disease (Appendix 15.5) at Screening.
11. The subject has any other disease or condition that would interfere with the interpretation of study assessments.
12. The subject has a musculoskeletal disorder (e.g., arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (e.g. cane or walker), or any disease that is likely to limit ambulation, or is connected to a machine that is not portable.
13. The subject has an unstable psychiatric condition or is mentally incapable of understanding the objectives, nature, or consequences of the trial, or has any condition which in the Investigator's opinion would constitute an unacceptable risk to the subject's safety.
14. The subject is receiving an investigational drug, has an investigational device in place, or has participated in an investigational drug or device study within 30 days prior to Screening.
15. The subject has chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 μmol/L) or the requirement for dialysis.
16. Subjects must not have 3 or more of the following left ventricular disease/dysfunction risk factors:
    i. Body Mass Index (BMI) ≥30 kg/m^2
    ii. History of essential hypertension
    iii. Diabetes mellitus – any type
    iv. Historical evidence of significant coronary disease established by any one of: history of myocardial infarction or percutaneous coronary intervention or angiographic evidence of coronary artery disease (>50% stenosis in at least one coronary artery), positive stress test with imaging, previous coronary artery bypass graft, stable angina

4.3 PRESCRIBED THERAPY

4.3.1 PAH-Approved Therapies

All subjects must be receiving a dose of one PAH-approved oral therapy that complies with the approved prescribing information (as described in Table 4-1) for the product for a minimum of 30 days and at the current dose for at least 10 days prior to randomization. All subjects must be willing to remain on the same background approved PAH oral therapy at the same dose for the duration of the study. In the event a subject must undergo a change in background therapy, they should be switched to another approved agent in the same medication class if possible. If another agent in the same class is not available, the subject should be switched to an agent from another class of approved PAH oral medications. If no alternative therapy is available, the subject will continue in the study until either a clinical worsening event has occurred, the subject withdraws from the study, or the study is completed/discontinued.

Table 4-1 Minimum Allowable Doses of Background PAH Oral Therapy

PAH-Approved Background Therapy	Dosing Schedule
ambrisentan	5 mg once daily
bosentan*	125 mg twice daily
macitentan	10 mg once daily
sildenafil	20 mg three times daily
tadalafil**	40 mg once daily
riociguat***	1 mg three times daily

* 62.5 mg twice daily is permitted if used per prescribing guidelines (e.g., subject weighs less than 40 kg or has elevated liver function tests)
** 20 mg once daily is permitted if used per prescribing guidelines (e.g., subject has mild or moderate renal insufficiency)
***0.5 mg three times daily permitted if used per prescribing guidelines (e.g. subject cannot tolerate hypotensive effects)

Prior to Week 24, if the Investigator, for any reason, initiates a second PAH-approved oral therapy in addition to the PAH-approved oral therapy initiated prior to Screening (e.g., due to disease progression without meeting the definition of clinical worsening as defined in Section 2.1), the subject must be discontinued from the study drug. The subject should be encouraged to remain in the study and attend all visits up to and including Week 24; however, the subject will not be eligible for enrollment in the open-label study (TDE-PH-311). After Week 24, if the Investigator initiates a second PAH-approved oral therapy due to any reason in addition to the PAH-approved oral therapy initiated prior to Screening, the subject must be discontinued from the study and will not be eligible for enrollment in the open-label study.

All changes in drug or dosage regimens during the study will be recorded in the subject's source documents and transcribed as required to the eCRF.

Product labeling for the background PAH-approved oral therapy should be consulted in order to guide the monitoring of AEs. The dose of study drug should be adjusted first in response to any new AEs that occur during the study, rather than adjusting the dose of PAH-approved oral therapy; unless the event is considered causally related to the PAH-approved oral therapy. If a subject meets the definition of clinical worsening during the study and receives only short term (28 days or less) treatment with an infused or inhaled PGI_2 therapy for worsening PAH, they will be permitted to enter the open-label extension study (TDE-PH-311). If a subject prematurely discontinues the study for any reason other than clinical worsening, or receives long-term (29 days or more) treatment with an infused or inhaled PGI_2 therapy for worsening PAH, they will not be permitted to enter the open-label extension study. During the course of the study, if the Investigator initiates a second PAH-approved oral therapy due to any reason (e.g. disease progression without meeting the definition of clinical worsening as defined in Section 2.1) in addition to the PAH-approved oral therapy initiated prior to Screening, the subject must be discontinued from the study and will not be eligible for enrollment in the open-label study (TDE-PH-311).

4.3.2 Concomitant Medications

All subjects must have been stabilized on optimal doses of conventional PAH therapies (e.g., oral vasodilators, digoxin, diuretics, oxygen, anticoagulants) for at least 10 days prior to Baseline assessments. The exceptions are the discontinuation or dose changes of anticoagulants and/or dose change of diuretics. After randomization, additions, deletions, and dose changes may occur if the Investigator determines it is medically necessary. For the purposes of the 6MWT, if the subject was assessed at Baseline using oxygen therapy then all future 6MWTs during the study must be conducted with the same oxygen flow rate and mode of administration; any changes in oxygen therapy administration should be noted in the eCRF.

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

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Eligible subjects will be randomly allocated to receive either UT-15C or placebo at randomization. During the Screening period a screening number will be assigned using an electronic data capture (EDC) system to identify individual subject data until the subject is randomized. Upon randomization, each subject will be assigned a new unique study subject number via the IVRS/IWRS. The IVRS/IWRS will also be responsible for allocation of all study drug.

5.2 RANDOMIZATION

The study will be randomized 1:1 UT-15C to placebo. All subjects will be randomly allocated to receive UT-15C or placebo through the IVRS/IWRS using a centrally administered stratified permuted block randomization by type of background therapy (Strata 1: PDE5-I and sGC stimulator; Strata 2: ERA) which will be balanced across the two treatment groups. Subjects will also be stratified by Baseline 6MWD (less than or equal to 350 meters and greater than 350 meters). Block sizes will be variable and not disclosed to Investigators so that no inferences can be made about possible treatment assignments of current or future subjects.

Prior to randomization, site personnel should complete a Pre-Baseline Review Form for review and approval by the Medical Monitor.

5.3 BLINDING

The Investigator, study site, subject, and sponsor will not be aware of the treatment allocation. All clinical trial material (CTM) will be provided as blinded study drug. See Section 6.2 for the procedure for unblinding subjects at the end of study to determine appropriate starting dose for the open-label study (TDE-PH-311).

6 DRUGS AND DOSING

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

The UT-15C tablets are sustained release osmotic tablets. Active treatment is UT-15C tablets provided as 0.125, 0.25, 0.5, 1, and 2.5 mg strengths. The 0.125, 0.25, 0.5, 1, and 2.5 mg tablets are colored blue, green, white, yellow, and pink, respectively. The formulation contains

pharmaceutically acceptable excipients used in other approved drug products. Placebo tablets are identical in size, shape, and color to the respective UT-15C tablets.

Once all entry criteria have been met and random treatment assignment confirmed, the first dose of study drug (0.125 mg) should be taken at the site by the subject immediately after (~10 minutes) consuming food. Oral dosing of study drug will be continued at 0.125 mg TID (every 6 to 8 hours) immediately after (~10 minutes) consuming food. Subjects must be instructed to take the appropriate amount of UT-15C tablets based upon their prescribed dose. Prior to the Week 4 visit, each dose of study drug should be adjusted in 0.125 mg increments every 24 hours as clinically indicated. Following the Week 4 visit throughout the remainder of the study, each dose of study drug may be adjusted in 0.125 or 0.25 mg increments every 24 hours as clinically indicated. The maximum allowable dose of study drug will be 12 mg TID.

Doses of study drug should continue to be increased in the absence of dose-limiting drug-related adverse effects, to ensure that each subject receives the optimal clinical dose throughout the study. Table 6-1 provides a range of doses that may be reasonable targets for a subject to achieve by visit notwithstanding any AEs that limit dose escalation.

Table 6-1 Study Drug Goal Dose Titration Ranges

Study Week	Dose (mg) Three Times Daily
4	0.5 – 1.5
8	1.5 – 2.5
12	2.5 – 3.5
24	5.5 – 6.5

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Each dose of study drug is not required to be the same during titration. For example, doses of 1.125 mg morning, 1.125 mg afternoon, and 1.25 mg evening, are acceptable during titration. It is recommended that the difference between any of the three doses not exceed 0.125 mg prior to Week 4 or 0.25 mg after Week 4.

At least weekly telephone calls between site personnel and the subject should be made during the first 24 weeks of the study to monitor AEs and make decisions about dose titration. More

frequent telephone calls may be necessary depending on the frequency of dose titration and to manage AEs or signs and symptoms of disease. If dose titration is considered appropriate, site personnel will instruct the subject to modify their dose. Study drug dosing should be recorded at each study visit between Baseline and Week 24. Dose changes between Baseline and Week 24 will be recorded in source documentation and the subject's eCRF by site personnel. Beyond Week 24, study drug dose will be recorded on the day of Continued Visits (e.g. Weeks 36, 48, etc.) and every 30 days between Continued Visits in source documentation and the eCRF by site personnel. If it becomes necessary for a subject to modify their dose (e.g., due to an AE) without prior instructions from site personnel, the subject should be instructed to contact the site as soon as possible and report any dose changes to site personnel for updating in source documentation and the eCRF as appropriate.

After Week 24, at least monthly telephone calls should be made to continue to monitor AEs and make decisions regarding appropriate dose titrations. More frequent telephone calls may be necessary depending on the frequency of dose titration and to manage AEs or signs and symptoms of disease. Site personnel should record all dose changes in source documentation from Week 24 until Study Termination.

In the event a subject requires to be permanently discontinued from study drug (e.g. as a result of clinical worsening or the subject wishes to withdraw from further participation in the study), the Investigator should conduct the study drug termination assessments and then gradually down titrate the study drug, taking into consideration the subject's clinical condition, current study drug dosing regimen, and previous clinical response to study drug.

Throughout the course of the study, the dose of study drug should continue to be increased at the discretion of the Investigator up to a maximum allowable dose of 12 mg TID. Dose escalation may be made less frequently or temporarily suspended if a subject experiences an intolerable AE that may worsen as a result of an increase in study drug dose. If an AE remains intolerable, the Investigator may decrease the dose of study drug. In the event of continued intolerable AEs, dose reductions may occur. The exact dose reduction and frequency of dose reduction should be based on the clinical condition of the subject and the severity/seriousness of the event. In general, dose reductions may occur in 0.125 mg or 0.25 mg increments every 12 to 24 hours.

Larger dose reductions may be necessary in the event of an emergency situation. If the subject is still experiencing an intolerable AE then the Investigator may temporarily or permanently withdraw the subject from study drug. Following temporary discontinuation of study drug, all attempts should be made to re-initiate study drug in affected subjects. Subjects should be re-started on study drug at a reduced dose or at 0.125 mg TID depending on the clinical condition of the subject, the subject's previous response to study drug, the dose at the time of discontinuation, and the duration of temporary discontinuation from study drug. Following restart of study drug, all efforts should be made to increase the dose until the desired clinical improvement in the subject's symptoms of PAH occurs.

Notwithstanding these study drug dosing guidelines, the well-being of each subject is paramount and all Investigators must act in accordance with the best medical interests of the subjects at all times during their participation in the study.

6.1.1 Dosing of Study Drug in Relation to Meals

Subjects should take study drug approximately every 6 to 8 hours with approximately 240 mL (8 ounces) of water or other beverage (e.g. juice, milk, soda, etc.) immediately after (~ 10 minutes) consuming food.

Subjects should be instructed to be careful not to break, chew, or disrupt the integrity of the tablet as this will result in inappropriate delivery of the active ingredient. If the tablet is inadvertently damaged during administration, the subject should contact site personnel in order to be monitored for the onset of symptoms due to possible overdose. Any tablet damaged during handling by the subject should not be consumed by the subject. The subject should be instructed to notify the study personnel and return the damaged study drug at the next scheduled visit.

6.1.2 Dosing and Administration of Adjunctive Medications

Every subject must be receiving one PAH-approved oral monotherapy (e.g., sildenafil, tadalafil, bosentan, ambrisentan, macitentan, or riociguat) for at least 30 days prior to randomization and on the same dose for at least 10 days prior to randomization. Dosing of background PAH-approved oral monotherapy must comply with the prescribing information for the product.

All attempts should be made to adjust the dose of study drug rather than the dose of PAH-approved oral therapy to obtain the desired clinical response. Throughout the course of the study, dose and frequency of the PAH-approved oral therapy may not be increased to compensate for lack of efficacy. Similarly, the dose and frequency of PAH-approved oral therapy should not be reduced during the study unless it is considered medically necessary to protect the safety of the subject. If the dose of PAH-approved oral therapy is inadvertently titrated during the course of the study, the dose should be titrated back to the dose used at the time of randomization, if medically appropriate. If the dose of PAH-approved oral therapy is increased during the Treatment Phase and is not subsequently titrated back to the dose used at the time of randomization, the subject will need to be removed from the study.

In the event a subject must undergo a change in background therapy, they should be switched to another agent in the same PAH-approved medication class if possible. If another agent in the same class is not available, the subject should be switched to an agent from another class of PAH-approved medication. If no alternative therapy is available, the subject will continue in the study until either a clinical worsening event has occurred, the subject withdraws from the study, or the study is completed/discontinued.

All subjects must have been stabilized on optimal doses of conventional PAH therapies (e.g., oral vasodilators, digoxin, diuretics, oxygen, anticoagulants) for at least 10 days prior to randomization. The exceptions are the discontinuation or dose changes of anticoagulants and/or dose change of diuretics. After randomization, additions, deletions, and dose changes may occur if the Investigator determines it is medically necessary.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, neither the site personnel, subject, nor sponsor should be unblinded to the treatment assignment of any subject for any reason except in the event of a medical emergency (e.g., a life threatening event), if and when knowledge of the treatment assignment is considered necessary to determine the optimal medical management. Appropriate communications should take place between the site and the sponsor before accessing the IVRS/IWRS to allow unblinding of a subject's treatment assignment. In the event of a medical emergency that requires immediate

unblinding, the IVRS/IWRS may be accessed by the Investigator to determine treatment assignment.

Subjects who remain on study drug, complete required study assessments, and meet the definition of clinical worsening will be eligible for an open-label study (TDE-PH-311). Subjects requiring long term treatment (29 days or more) with infused or inhaled PGI_2 for treatment of worsening PAH are not eligible for the open-label study. Following completion of the Study Drug Termination assessments for a subject (see Table 3-1) and entry of required data into the IVRS/IWRS, the site personnel will be unblinded to that subject's treatment assignment. If the subject received UT-15C during the study then the subject may remain on the same dose of study drug upon entry into the open-label study. If the subject received placebo during the study then the subject should start treatment with UT-15C in the open-label study in accordance with that protocol.

Subjects who permanently discontinue study drug for any reason other than meeting the definition of clinical worsening are not eligible for entry into the open-label study. The site personnel will not be unblinded to the treatment assignment of these subjects unless required for safety reasons.

Following completion of all Study Drug Termination assessments (see Table 3-1) and entry of required data into the IVRS/IWRS, the site personnel will be unblinded to that subject's treatment assignment at the time of enrollment into the open-label study. After approximately 205 adjudicated clinical worsening (morbidity or mortality) events have occurred, all ongoing subjects will be eligible for enrollment in the open-label study or gain access to drug commercially if approved.

6.3 COMPLIANCE

The Principal Investigator or other site personnel under the direction of the Principal Investigator will be responsible for dose titration of study drug and recording all dosing information in source documents. During telephone calls, site personnel will record the current dose of study drug and determine if the subject is taking study drug as prescribed.

Each subject will be provided with a dosing diary in order to record dosing information from Randomization until Week 24; the use of the dosing diary is optional after Week 24. At scheduled study visits, subjects should be instructed to bring all study drug (including empty and unused bottles) and their dosing diary to the investigational site. Upon return of study drug and dosing diary at the Week 4, 8, 12, and 24 visits, the study coordinator or pharmacist must document the number of returned tablets of each strength and determine if the appropriate amount of study drug remains based upon the dose of study drug prescribed. Each subject will also be asked at each visit whether he or she has been compliant with dosing instructions. Subject compliance with the prescribed dosage regimen will be monitored throughout the study. If it is determined that a subject is not compliant with study drug then site personnel must re-educate the subject on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor.

Upon return of study drug at all protocol-required on-site study visits (e.g. Weeks 4, 8, 12, 24, etc.), all bottles of study drug will be collected. Study drug returned will not be re-dispensed to the subject. Site personnel will dispense a new supply of study drug at each protocol-required visit for the subsequent interval. If necessary, additional study drug may be dispensed in between protocol-required visits.

7 EXPERIMENTAL PROCEDURES

7.1 SCREENING PHASE

Sites may conduct pre-Screening activities prior to a specific subject signing an informed consent. Pre-Screening activities may include review of the site's database to identify potential patients that may be eligible for the study. The Screening Phase will be conducted within 30 days prior to randomization and after informed consent has been obtained. The Screening and Baseline assessments may be conducted in one visit if all assessments are performed and all entry criteria are satisfied within the 48 hours prior to randomization and dosing with study drug.

The recommended sequence of events for Screening assessments are displayed below:

- Informed consent
- Inclusion/exclusion criteria
  - If necessary, the following procedures may be performed during the 30 day Screening window if required to satisfy inclusion/exclusion criteria.
    - RHC
    - Echocardiography
    - Ventilation Perfusion Scan
    - High Resolution Computerized Tomography (CT) Scan
    - Multigated angiogram (MUGA)
    - Pulmonary Angiography
    - Pulmonary Function Tests
  - Previous medical records documenting eligibility criteria may also be used provided the previous records document subject eligibility within the protocol mandated timelines, as applicable.
- Demographics
- PAH history
- Medical history
- Vital signs (following at least 5 minutes of rest)
- Physical examination
- 12- lead ECG (following at least 5 minutes rest in the semi-recumbent position)
- Practice 6MWT/Borg dyspnea score (*optional*; serves as a practice test if the subject has not previously performed this test at the study site; 6MWT to be conducted following at least 5 minutes of rest and Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical laboratory tests
- Urine pregnancy test (for WOCBP)
- Concomitant medications
- AE assessment
- Complete and submit Pre-Baseline Review Form

7.2 BASELINE VISIT

The recommended sequence of events for the Baseline Visit is displayed below:

- RHC (optional; must be performed within 5 days before randomization (inclusive) and on one stable PAH-approved oral monotherapy for a minimum of 10 days prior to RHC)
- Confirmation of inclusion/exclusion criteria
- Vital signs (following at least 5 minutes of rest); including height
- WHO Functional Class for PAH
- AE assessment
- 6MWT/Borg dyspnea score (6MWT to be conducted following at least 5 minutes of rest; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical laboratory tests/NT-proBNP
- Urine pregnancy test (for WOCBP)
- Randomization (to be performed after all other Baseline assessments are completed)
- First administration of study drug immediately (~10 minutes) after consuming food
- Drug accountability
- Concomitant medications
- At least weekly telephone calls begin following initiation of study drug up to Week 24 of treatment, to monitor compliance, AEs, use of concomitant medications, occurrence of clinical worsening and to make decisions regarding dose titration

7.3 TREATMENT PHASE

Weeks 4, 8, 12, and 24 assessments are listed below (in the recommended order):

- Vital signs (following at least 5 minutes of rest)
- WHO Functional Class for PAH
- AE assessment
- Drug accountability/compliance
- 12-lead ECG (Week 24 only; following at least 5 minutes rest in the semi-recumbent position)
- Concomitant medications
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after last dose of study drug and following at least 5 minutes of rest; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment
- Urine pregnancy test (for WOCBP)
- Clinical laboratory tests/NT-proBNP (Weeks 12 and 24 only)
- Continue administration of study drug and dose titration

- Continue at least weekly telephone contact (study drug dose at Weeks 16 and 20 must be recorded in the eCRF; at least monthly telephone contact initiated at Week 24)
- RHC (optional - Week 24 only; to be conducted within 72 hours following all other Week 24 assessments; as best as possible to be performed 3 to 6 hours after previous dose of study drug)

Continued Visits beyond Week 24 assessments include (in the recommended order):

- Vital signs (following at least 5 minutes of rest)
- WHO Functional Class for PAH
- AE assessment
- Drug accountability/compliance
- Concomitant medications
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after last dose of study drug and following at least 5 minutes of rest; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment
- Clinical laboratory tests/NT-proBNP (at the first Continued Visit and every other Continued Visit thereafter, e.g., Continued Visits #3, #5, #7, etc.)
- Urine pregnancy test (for WOCBP)
- Continue administration of study drug and dose titration
- Continue at least monthly telephone contact (study drug dose should be recorded in the eCRF on the day of Continued Visits (e.g. Weeks 36, 48, etc.) and every 30 days between Continued Visits)

Table 7-1 Continued Visits by Week Beyond Week 24

Continued Visit	Corresponding Study Week*
#1	36
#2	48
#3	60
#4	72
#5	84
#6	96
#7	108
#8	120
#9	132
#10	144
#11	156
#12	168
#13	180

Continued Visit	Corresponding Study Week*
#14	192
#15	204
#16	216
#17	228
#18	240

* Visit window is ±14 days

Unscheduled Visits

Subjects may return to the study site at any time for additional assessments, including but not limited to clinical worsening, 6MWTs/Borg dyspnea score, AEs, or dispensing of additional study drug.

7.4 STUDY DRUG TERMINATION VISIT

Subjects will continue in the study until they experience clinical worsening, prematurely discontinue the study for any reason, or approximately 205 adjudicated clinical worsening events have occurred. If a subject remains ongoing with study treatment at the time when approximately 205 adjudicated clinical worsening events have occurred, the Study Drug Termination Visit should be scheduled as soon as possible. The following assessments will be conducted immediately after the decision is made to discontinue study drug (prior to down titration).

- Vital signs (following at least 5 minutes of rest)
- Physical examination
- Clinical worsening assessment
- WHO Functional Class for PAH
- AE assessment
- Drug accountability/compliance
- 12-lead ECG (following at least 5 minutes rest in the semi-recumbent position)
- Concomitant medications
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after last dose of study drug and following at least 5 minutes of rest; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- Clinical laboratory tests/NT-proBNP

- Collection of blood sample for evaluation of blood biomarkers (optional)
- Collection of urine sample for evaluation of urine biomarkers (optional)
- Collection of blood sample for evaluation of pharmacogenomics (optional)

If the subject permanently discontinues study drug prior to Week 24 for any reason other than clinical worsening (e.g., AEs, addition of second PAH-approved oral therapy), the subject should immediately complete the study drug termination visit assessments and be encouraged to remain in the study and complete all visits up to and including Week 24. The Study Drug Termination Visit assessments should be conducted immediately after the decision is made to discontinue study drug (prior to down titration).

7.5 ACCESS TO THE OPEN-LABEL STUDY

Subjects who discontinue the study due to clinical worsening as reviewed by the Medical Monitor and undergo Study Drug Termination assessments will be eligible for the open-label extension study (TDE-PH-311) unless long-term (29 days or more) treatment with an infused or inhaled PGI_2 was initiated. Subjects who prematurely discontinue the study for any reason other than clinical worsening (e.g., AEs, withdrew consent, etc.) will not be eligible for entry into the open-label study.

Subjects who remain on study drug at the time that approximately 205 adjudicated clinical worsening events have occurred and complete Study Drug Termination assessments will be eligible for entry into the open-label extension study (TDE-PH-311) or may gain access to commercial drug if approved.

If a subject is eligible for the open-label extension study and received UT-15C during the blinded study then the subject may remain on the same dose of study drug upon entry into the open-label study. If the subject received placebo during the blinded study then the subject should start treatment with UT-15C in the open-label study in accordance with that protocol.

An IVRS/IWRS will be utilized to record appropriate efficacy data prior to providing each individual subject's treatment assignment to appropriate site personnel in order to start each subject on the appropriate dose of UT-15C in the open-label study.

See protocol TDE-PH-311 for more details regarding the open-label extension trial.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or will be withdrawn from the study and/or study drug 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 study drug to protect the safety of the subject
- The subject violated the protocol
- The subject's behavior is likely to undermine the validity of his/her results
- The subject experiences clinical worsening
- The subject becomes pregnant

If a subject is discontinued from the study prematurely, the Investigator will complete the End of Study Record for that subject and provide an explanation, if needed. For subjects who meet the definition of clinical worsening, the site must complete the specified eCRF page (see Section 3.2.1.1). If study drug has been administered, the Investigator should make every effort to perform all Study Drug Termination Visit assessments prior to study drug dose down-titration and study discontinuation.

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. 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.

The end of the study (study completion) will be declared and subjects will be transitioned out of the study based on the Data Monitoring Committee (DMC) and Sponsor's decision following the interim analysis, or approximately 205 adjudicated clinical worsening events have occurred, or the sponsor stops the study for any other reason.

8.3 CRITERIA FOR DISCONTINUING THE SITE

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

- The Principal Investigator elects to discontinue the study
- The sponsor elects to discontinue the study at the site
- Applicable regulations are not observed
- The protocol is repeatedly violated or critical violations are documented
- 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 a clinical trial whether or not it is related to the study drug. An AE may include 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. AEs may also include worsening of an existing symptom or condition or pre/post-treatment events that occur as a result of protocol-mandated procedures.

9.1.2 Serious Adverse Event

An SAE is an AE occurring at any dose 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 one 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.

Planned hospitalization for elective treatment or procedure for a pre-existing condition that did not worsen from the time of randomization (e.g. routine RHC) is not considered an SAE and does not meet the definition for clinical worsening.

9.1.3 Adverse Events Associated with Progression of PAH

Expected events that are related to the progression of a subject's PAH are defined in Appendix 15.6. All events that occur during the course of the study that are included on this list and felt to be related to the progression of the disease by the Investigator should not be recorded as AEs in the eCRF as these PAH symptoms will be evaluated and recorded as an efficacy endpoint and/or will be captured as disease related events.

However, an event must be recorded as an AE/SAE in the eCRF, if it meets one or more of the following criteria:

- There is a reasonable possibility that it may have been caused by study drug.
- It is serious.
- It has occurred at greater than expected severity (intensity, frequency, or duration).

9.2 DOCUMENTATION OF ADVERSE EVENTS

AEs will be captured from the time the ICF is signed. An AE or SAE occurring during the study, following completion of the ICF, 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 15.4 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 pre-randomization values), until they are judged by the Investigator to no longer be clinically significant, or for up to 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.

9.2.1 Clinical Worsening Events

Clinical worsening events for this study include all clinical worsening (morbidity or mortality) events that meet the definition for clinical worsening (Section 3.2.1.1). When these events occur, they must be documented in the subject's source documents and on the specified page of the eCRF and should be electronically submitted using the electronic eCRF platform within 48 hours after the event becomes known to the Investigator or designee. The Medical Monitor will review the event and correspond with the Investigator and site, as appropriate. Although subjects may be discontinued from the study for medical necessity at any time, subjects should not be discontinued for a clinical worsening event until the event has been reviewed by the Medical Monitor. Any clinical worsening event that is also an SAE(s) will be reported per the guidelines as specified in Sections 9.2 and 9.3.

9.3 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the sponsor within 24 hours of awareness by fax [redacted] or e-mail [redacted]. A completed SAE report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corporation. A follow-up SAE report form must be forwarded to Global Drug Safety at United Therapeutics Corporation within 48 hours of the receipt of any new/updated information. The Investigator must also promptly notify their Investigational Review Board (IRB) or Ethics Committee (EC) of the SAE, including any follow-up

information, in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

9.4 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 Form and either faxing or e-mailing this form to Global Drug Safety at United Therapeutics Corporation [redacted]. Subjects who become pregnant during the trial will be withdrawn from active participation in the trial and will discontinue study drug after an appropriate period of down-titration.

United Therapeutics Global Drug Safety will follow up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to request the Investigator to complete a Pregnancy Outcome Report Form. Pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, a termination for medical reasons other than PAH, or a congenital anomaly in the offspring.

9.5 SAFETY REPORTS

In accordance with national regulations, the sponsor or designee, will notify the regulatory agencies, Investigators, and/or IRBs and ECs of all relevant AEs (usually those that are considered to be possibly attributable to study drug and are both serious and unexpected) in accordance with the applicable national regulations. The Investigator must report these SAEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

Subject data will first be documented in the subject's source documents, and then transferred into the eCRF. Site personnel will be responsible for recording all subject data into the eCRF. Data for any subject who signs an ICF will be captured in the eCRF. The eCRF screens are to be reviewed by the Principal Investigator for completeness and accuracy. The Principal

Investigator must sign each subject's eCRF to signify their approval of the data. The database will be final when final query resolution has been completed and all data management quality control procedures are complete.

10.2 SAMPLE SIZE

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

Based on the results of other PAH studies, (e.g., AMBITION [ambrisentan and tadalafil] and GRIPHON [selexipag]; Galiè, 2015; Sitbon, 2015) an interim analysis for efficacy is planned when 75% of the total adjudicated worsening events have occurred. In order to control the total alpha at a two-sided 0.05 level, the method of Lan and DeMets with O'Brien-Fleming-type alpha spending function will be used to calculate the boundaries for stopping the study for efficacy at the interim analysis [Lan and DeMets, 1983]. If the interim analysis is performed with 154 events, the boundary on the p-value scale will be 0.020 and 0.044 for the final analysis. Calculations will be performed in EAST version 6.4, Cytel Inc, using simulated power.

If enrollment continues beyond the interim efficacy analysis, final enrollment will be stopped when approximately 190 clinical worsening (morbidity or mortality) events have been reported by Investigators and reviewed by the Medical Monitor. Subjects will be followed until the occurrence of approximately 205 adjudicated clinical worsening events, at which time all remaining subjects will be transitioned to the open-label extension study. No more than 850 subjects will be enrolled.

10.3 ANALYSIS PLAN

Details of various efficacy and safety analyses are provided below. Further details will be documented in a statistical analysis plan prior to any unblinding of study data by the sponsor. All statistical calculations will be done using the latest version of SAS (currently version 9.2).

The Intent-to-Treat (ITT) population will be defined as all subjects randomized into the study that receive at least one dose of study drug; all subjects will be counted as being in the group to which they were randomized, regardless of the treatment they were actually given. All efficacy analyses will be performed on this ITT population. Additional efficacy analyses may be performed on further populations to be defined in a detailed statistical analysis plan.

10.3.1 Primary Efficacy Endpoint

The primary hypothesis is that PAH-approved oral monotherapy in combination with UT-15C will prolong the time to clinical worsening when compared with PAH-approved oral monotherapy in combination with placebo in subjects with PAH. The primary efficacy endpoint will be tested at an interim analysis when 75% of total adjudicated events have occurred with an alpha spending of 0.020 and at the final analysis at an alpha of 0.044 with the overall Type I error rate at 0.05. Efficacy boundaries for early stopping of the trial for efficacy is calculated based on O'Brien-Fleming alpha-spending function.

10.3.2 Secondary Efficacy Endpoint(s)

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

1. Exercise capacity as assessed by 6MWD measured at Week 24
2. NT-proBNP at Week 24
3. Combined 6MWD/Borg dyspnea score at Week 24

In order to control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed-sequence) testing procedure. The 6MWD at Week 24 will be tested at a two-sided Type I error rate of 0.05. The subsequent tests for NT-proBNP at Week 24 and then the combined 6MWD/Borg dyspnea score at Week 24 will be tested only if the preceding test is statistically significant. All other secondary endpoints will be summarized using descriptive statistics or analyzed using an exploratory approach.

10.3.2.1 Borg Dyspnea Score

The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT. Scores range from 0 (for the best condition) to 10 (for the worst condition). The difference between treatment groups for the change from Baseline to each follow-up assessment will be tested using the Wilcoxon rank-sum test.

10.3.2.2 Combined 6MWD and Borg Dyspnea Score

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

1. Standardized mid-ranks of walk distance will be calculated as described for the analysis of 6MWD;
2. Standardized mid-ranks of Borg dyspnea score will be calculated in an analogous manner;
3. The standardized mid-ranks for walk distance and for Borg dyspnea score will be combined by calculating their arithmetic average;
4. A Cochran-Mantel-Haenszel mean score test will be used on the standardized mid-ranks of these combined ranks.

10.3.2.3 WHO Functional Class for Pulmonary Hypertension

Changes from Baseline to each follow up assessment in WHO Functional Class will be summarized and compared between treatment groups using the Wilcoxon rank-sum test.

10.3.2.4 N-terminal pro-BNP

Changes from Baseline to each follow up assessment in plasma NT-proBNP will be summarized and compared between treatment groups.

10.3.2.5 Hemodynamics (optional)

Changes from Baseline to Week 24 in hemodynamic parameters as assessed by RHC will be summarized and compared between treatment groups.

10.3.3 Exploratory Endpoints

The following parameters will be evaluated:

- Optional evaluation of biomarkers
- Optional evaluation of pharmacogenomics

10.3.4 Safety Analyses

The safety population will be defined as all subjects in the study that receive study drug, and all subjects will be counted as being in the group corresponding to the treatment that they actually received. If a subject received UT-15C at any point during the study, they will be counted in the UT-15C treatment group within the safety population. All safety analyses will be performed on the safety population.

The safety of UT-15C will be evaluated by comparisons of AEs, clinical laboratory parameters, and vital signs in the two treatment groups. All AEs as recorded by the Investigators will be assigned MedDRA preferred terms by the sponsor for reporting purposes. For all safety endpoints, tabular summaries will be provided.

10.4 INTERIM ANALYSIS

Interim safety analyses are intended to be performed after approximately 200, 400, and 600 subjects are enrolled in the study, or ad hoc per request of the independent DMC, as necessary (see Section 10.7).

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

All interim analyses for safety and efficacy will be performed by a statistical group independent of the study conduct. All unblinded results will only be reviewed by the independent DMC members.

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.

10.7 DATA MONITORING COMMITTEE

A DMC will be established for the study, composed of up to five independent members including physicians knowledgeable in the treatment of PAH and a statistician. Throughout the course of the study, the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur after approximately 200, 400, and 600 subjects are enrolled in the study or ad hoc per request of the DMC, as necessary. In addition, the DMC will review the interim analysis results for efficacy data when 75% (corresponding to 154 events) of the total approximately 205 adjudicated clinical worsening (morbidity and mortality) events have accrued. The DMC will be blinded to individual subject treatment allocation during the review process. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The DMC will also review the formal interim analysis results and recommend continuation or early termination of the study based on stopping criteria defined in the DMC charter. The sponsor will only have access to blinded study data until the database lock for the primary analysis.

10.8 CLINICAL WORSENING ADJUDICATION COMMITTEE

An adjudication committee, comprised of at least three members, including physicians knowledgeable in the treatment of PAH, has been established for the study. Members of the adjudication committee are independent of the DMC and cannot participate as Investigators in this study. The adjudication committee will be blinded to individual subject treatment allocation during the review process. If the adjudication committee does not agree with an Investigator's assessment of clinical worsening for a given subject, this subject will not be included in the analysis and their worsening event will not count towards the total number of adjudicated events needed to complete the study.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics Corporation will supply study drug (UT-15C and placebo) for administration during the study. The UT-15C tablets are sustained release osmotic tablets. Active treatment will be UT-15C tablets provided as 0.125, 0.25, 0.5, 1, and 2.5 mg strengths for the study. Each tablet contains either 0.125 mg treprostinil (equivalent to 0.15875 mg treprostinil diethanolamine), 0.25 mg treprostinil (equivalent to 0.3175 mg treprostinil diethanolamine), 0.5 mg treprostinil (equivalent to 0.635 mg treprostinil diethanolamine), 1 mg of treprostinil (equivalent to 1.27 mg treprostinil diethanolamine), 2.5 mg of treprostinil (equivalent to 3.17 mg treprostinil diethanolamine), or no treprostinil (placebo). The 0.125, 0.25, 0.5, 1, and 2.5 mg tablets are colored blue, green, white, yellow, and pink, respectively. UT-15C tablets and matching placebo tablets will be provided in child resistant bottles each containing 100 tablets.

11.2 LABELING

Each bottle and/or kit will be labeled in accordance with applicable national regulations, to include at least the following information: study drug, trial reference code, strength, quantity, route of administration, manufacture or expiry date, lot number, sponsor name, address and telephone number, and storage conditions. The labels on the bottles may include blank fields for sites to document the following information specific to each bottle, including but not limited to, Investigator name, subject number/initials, and date dispensed.

11.3 STORAGE AND HANDLING OF CTM

All study drug will be stored at room temperature (do not store above 25°C with excursions permitted up to 30°C). Study drug should not be frozen, refrigerated, or exposed to heat. Site personnel should refer to investigational medicinal product labeling or regulatory submissions for specific requirements by country or region in accordance with local regulations or guidance.

Study drug at the investigational site will be stored in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study drug to any person not participating in this study.

The pharmacist or appropriate personnel at the investigational site will deliver and retrieve each assigned bottle to the subject at each study visit as needed for use during the course of the study. Subjects should be instructed to return all study drug, including empty bottles, to the appropriate study personnel at every protocol-required visit.

11.4 SUPPLY AND RETURN OF CTM

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At Randomization, an IVRS/IWRS will be utilized by site personnel to randomize each subject and assign the appropriate study drug bottles for the first 4-week treatment interval. At subsequent visits to the clinic the IVRS/IWRS will be utilized by site personnel to assign new study drug bottles to each subject based upon their current dose of study drug and the length of time until the next protocol-required visit. Additional study drug supply may occur between protocol-required visits as required. At each protocol-required study visit all unused study drug dispensed to the subject should be returned to the study site (including empty and unopened bottles).

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records will be maintained during the study and these records will include: the amount of study drug received from the sponsor, the amount dispensed to each subject, and the amount of unused drug. At each visit, site personnel should assess drug dispensed, drug returned, and dosing information to confirm drug accountability and compliance. Once a representative from the sponsor is able to confirm drug accountability for that subject, study drug will be returned to a sponsor designated location for destruction. Study drug will not be destroyed on-site by the study staff or in the pharmacy.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 ICH GCP AND APPLICABLE NATIONAL REGULATORY REQUIREMENTS

The study will be conducted in accordance with ICH GCP guidelines and all applicable national regulations. The sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual development safety update report will be compiled by the sponsor for submission to those regulatory authorities and

IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, 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 authorized 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 ICF 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/EC and provide the sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's ICF and any other written information provided to the subject's 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/EC 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/EC approval of these amended documents prior to implementation. Copies of the IRB/EC 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/ECs that require it.

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

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical trial, the following documents (at minimum) will be provided to the site: Investigators' Brochure, Protocol, ICF, Budget Agreement, and access to the eCRF.

The site will be required to provide the following documents (at minimum) to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/EC Composition and Roster, IRB/EC protocol and ICF approval letters, Curriculum Vitae of study staff listed on the Form FDA 1572, and authorized clinical trial agreement (as required).

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, regulatory bodies, and the IRB/EC 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/EC or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A unique number will be assigned to all subjects and any report published will not identify the subjects by name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially adversely 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 United Therapeutics Corporation or its designee and the Investigator.

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

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/EC 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 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. For Investigators in the European Economic Area (EEA), the study records should be maintained for at least 15 years after study discontinuation. The Investigator must notify United Therapeutics Corporation before any disposal or change in location of study records.

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH GCP guidelines, monitors for United Therapeutics Corporation 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 must agree 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. In addition, auditors for United Therapeutics Corporation or its designee may periodically contact the site and conduct on-site visits.

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15 APPENDICES

15.1 PROCEDURE FOR 6-MINUTE WALK EXERCISE TEST AND BORG DYSPNEA SCALE

General Procedures

The 6 minute walk exercise test should be administered by the same tester and on the same course at each study site throughout the study for a given subject. 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 guidelines; 2002].

The area used for the 6 minute walk test should be pre-measured at approximately 30 m in length (but no shorter than 15 m [16 yards or 50 feet] in length at minimum) and at least 2 to 3 m in width. There should be no turns or curves to the 6 minute walk area. The length should be marked with gradations at least every 3 meters 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. At the end of 6 minutes, the tester will call "stop" while simultaneously stopping the watch and then measure the distance walked. The Borg dyspnea rating will be administered immediately following completion of the 6MWT.

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 six minutes. You will start from this point and follow the hallway to the marker (e.g. 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?"
"Please explain to me what you are going to do."

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 2 and 4 minutes by saying:

"You have completed 2 minutes."

And then by saying:

"You have completed 4 minutes."

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

Following the walk, the person administering the test will obtain a rating of dyspnea using the Borg Scale. The person will use the following dialogue:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life before, choose a number greater than 10 that represents how short of breath you feel. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between. For example, if you had shortness of breath somewhere between 4 and 5, you could choose 4 ½.

15.2 WHO FUNCTIONAL CLASSIFICATION FOR PULMONARY HYPERTENSION

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. These subjects are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These subjects manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

15.3 CLINICAL LABORATORY PARAMETERS

Blood Chemistries	Hematology	Other
Sodium	Red Blood Cell Count	NT-proBNP (plasma)
Potassium	Hemoglobin	Urine dipstick analysis*
Chloride	Hematocrit	Urine pregnancy test**
Bicarbonate/CO_2	Platelet Count	CD4 lymphocyte count****
Albumin	White Blood Cell Count	
Blood Urea Nitrogen/Urea		
Total Bilirubin		
Indirect Bilirubin		
Direct Bilirubin		
Alkaline Phosphatase		
Alanine Aminotransferase (ALT)		
Aspartate Aminotransferase (AST)		
Gamma-glutamyl transferase (GGT)		
Creatinine		
Thyroid Stimulating Hormone (TSH)*****		
Thyroxine (T4; free) if TSH is abnormal *****		

Visit Test Schedule

Visit	Labs Collected
Screen***	Chemistries, Hematology, TSH*****, CD4****, Urine dipstick, urine pregnancy**
Baseline***	Chemistries, Hematology, NT-proBNP, urine pregnancy**
Weeks 4 and 8	Urine pregnancy**
Week 12	Chemistries, Hematology, NT-proBNP, urine pregnancy**
Week 24	Chemistries, Hematology, NT-proBNP, urine pregnancy**
Continued Visits 1, 3 etc.	Chemistries, Hematology, NT-proBNP, urine pregnancy**
Continued Visits 2, 4, etc	Urine pregnancy**
Study Drug Termination Visit	Chemistries, Hematology, NT-proBNP, Urine dipstick, Urine pregnancy**

* pH, specific gravity, presence of protein or blood

** Urine pregnancy tests for WOCBP

*** If combining Screening and Baseline visit, utilize Baseline laboratory kit

**** At screen only; only for subjects with known HIV infection

***** If abnormal, free T4 will be automatically assessed at the central laboratory

15.4 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Principal 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?"

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

A serious AE 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 a serious AE when, based upon appropriate medical

judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

CAUSALITY

An estimate of causality between a specified AE and the study drug is made by the Investigator. Definitions of the categories follow:

- 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
- POSSIBLE - there is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear
- PROBABLE - there is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required

ACTION TAKEN

TEST AGENT DOSE MODIFICATION*

- Dose Increased - the dose or regimen of the test agent was increased
- Dose Not Changed - the dose or regimen of the test agent was not changed
- Dose Reduced - the dose or regimen of the test agent was decreased
- Drug Interrupted - administration of the test agent was stopped temporarily
- Drug Withdrawn - administration of the test agent was stopped permanently and not restarted
- Unknown - changes to the administration of the test agent cannot be determined

*NOTE: Only the last test agent action should be recorded in the eCRF.

OUTCOME

- Fatal - The study subject died
- Not Recovered/Not Resolved - The AE was ongoing
- Recovered/Resolved - The AE resolved
- Recovered/Resolved with Sequelae - The AE is considered resolved however there is a residual sequelae
- Recovering/Resolving - The AE is improving but is not yet completely recovered/resolved
- Unknown - The outcome of the AE cannot be determined

15.5 CHILD-PUGH SCORE

Parameter	Points		
	1	**2**	**3**
Hepatic encephalopathy	None (absent)	Stage I-II (mild or suppressed with medication)	Stage III-IV (severe or refractory)
Ascites	None (absent)	Mild-moderate (suppressed with medication)	Moderate-severe (refractory)
Bilirubin (total) µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (s)/INR	<4/(<1.7)	4-6/(1.71-2.20)	>6/(>2.20)

Class A (mild) = 5-6 points

Class B (moderate) = 7-9 points

Class C (severe) = 10-15 points (subjects in this class are excluded from participation)

15.6 EXPECTED EVENTS ATTRIBUTABLE TO THE PROGRESSION OF PULMONARY ARTERIAL HYPERTENSION (SYSTEM ORGAN CLASS AND PREFERRED TERM, VER. 16.0)

Abdominal pain (Gastrointestinal disorders; ABDOMINAL PAIN)	Hemoptysis (Respiratory, thoracic & mediastinal disorders; HAEMOPTYSIS)
Anorexia (Metabolism and nutrition disorders; ANOREXIA)	Hypoxia (Respiratory, thoracic & mediastinal disorders; HYPOXIA)
Ascites (Gastrointestinal disorders; ASCITES)	Loss of consciousness (Nervous system disorders; LOSS OF CONSCIOUSNESS)
Cardiac arrhythmia (Cardiac disorders; ARRHYTHMIA)	Nausea (Gastrointestinal disorders; NAUSEA)
Cardiac arrest (Cardiac disorders; CARDIAC ARREST)	Edema (General disorders and administration site conditions; OEDEMA)
Heart failure (including exacerbation of) (Cardiac disorders; CARDIAC FAILURE)	Orthopnea (Cardiac disorders; ORTHOPNOEA)
Chest pain (General disorders and administration site conditions; CHEST PAIN)	Pallor (Vascular disorders; PALLOR)
Cardiovascular collapse (Vascular disorders; CIRCULATORY COLLAPSE)	Palpitations (Cardiac disorders; PALPITATIONS)
Cor pulmonale (Cardiac disorders; COR PULMONALE)	Cool extremities (General disorders and administration site conditions; PERIPHERAL COLDNESS)
Cough (Respiratory, thoracic & mediastinal disorders; COUGH)	Pulmonary arterial hypertension, exacerbation of (Vascular disorders; PULMONARY ARTERIAL HYPERTENSION)
Cyanosis (Cardiac disorders; CYANOSIS)	Sudden death (Cardiac disorders; SUDDEN DEATH)
Dizziness (Cardiac disorders; DIZZINESS)	Syncope (Cardiac disorders; SYNCOPE)
Dyspnea at rest (Respiratory, thoracic & mediastinal disorders; DYSPNOEA)	Vasovagal reaction (Nervous system disorders; SYNCOPE VASOVAGAL)
Dyspnea on exertion (Respiratory, thoracic & mediastinal disorders; DYSPNOEA EXERTIONAL)	Tachycardia (Cardiac disorders; TACHYCARDIA)
Paroxysmal nocturnal dyspnea (Cardiac disorders; DYSPNOEA PAROXYSMAL NOCTURNAL)	Vomiting (Gastrointestinal disorders; VOMITING)
Exercise intolerance (General disorders and administration site conditions; EXERCISE TOLERANCE DECREASED)	Weight loss (Investigations; WEIGHT DECREASED)
Fatigue (General disorders and administration site conditions; FATIGUE)	Weight gain (Investigations; WEIGHT INCREASED)

15.7 A SUB-STUDY TO COLLECT THE VITAL STATUS OF SUBJECTS WHO DISCONTINUE FROM THE STUDY OR OPEN-LABEL EXTENSION STUDY (TDE-PH-311)

A Sub-study to Collect the Vital Status of Subjects Who Discontinue from the Study or Open-Label Extension Study (TDE-PH-311)

1 BACKGROUND AND RATIONALE

Even though subjects may discontinue from the study or open-label extension study (TDE-PH-311) for a variety of reasons, it is important to continue collecting vital status data on such subjects until the study is completed. Collection of the vital status data will allow an intention-to-treat overall survival analysis to be conducted using actual rather than imputed vital status data. This will be a separate analysis from the primary and secondary efficacy analysis and will provide supportive data for regulatory filings of oral treprostinil.

If and when a subject discontinues from the study or open-label extension study (TDE-PH-311), attempts should be made to obtain their consent to record their vital status up to the date of final completion of the study (i.e., when all patient have exited the study). Attempts should be made to collect survival data on all subjects, even those who are apparently lost to follow-up.

2 OBJECTIVE

To collect vital status data for subjects who discontinue from the study or open-label extension study (TDE-PH-311) to support an overall survival analysis of study participants

3 EXPERIMENTAL PLAN

Vital status for subjects who discontinue from the study or open-label extension study (TDE-PH-311) will be assessed every 6-months from their date of discontinuation via telephone calls and/or other methods as described below for the duration of the study. The data will continue to be collected in this study until the last subject has exited from the study.

Subjects are considered to have discontinued from the study if and when they discontinue and do not enroll into the open-label extension study (TDE-PH-311). Subjects are considered to have prematurely discontinued from the open-label extension study (TDE-PH-311) if they discontinue before the completion of the study (i.e., before the last subject has exited the study).

4 ESTIMATED STUDY DURATION

Vital status data will be collected every 6 months beginning from the date that each subject discontinues either the study or open-label extension study (TDE-PH-311) until the last subject exits the study.

5 DATA COLLECTION AND FOLLOW-UP OF SUBJECTS

Survival status for discontinued subjects will be collected every 6 months from the date of discontinuation via telephone calls or other methods as described below. The collection of vital status should include whether or not the subject is alive.

- If dead, the date of death must be obtained.
- If alive, the last known date the subject was confirmed to be alive must be provided.
- For those subjects who are lost to follow-up, the last known date that the subject was confirmed to be alive will be their date of the last contact with the site.

Methods to confirm subjects' survival status other than the recommended telephone calls every 6 months, may include and are not limited to, in-person study visits, searching of hospital records, and searching local and/or national public registries following applicable laws and regulations.

Any AEs that are spontaneously reported by the subject that occur on the commercially-available United Therapeutics drug should not be submitted as part of the study, rather, they will be subject to AE/SAE reporting under local government post-marketing AE/SAE reporting requirements.

6 STATISTICAL CONSIDERATIONS

Vital status data collected from subjects who discontinue from the study or open-label extension study (TDE-PH-311) will be combined with the data collected during the study and the open-label extension study (TDE-PH-311) for sensitivity analysis of overall survival. Vital status data collection from subjects who have discontinued the study minimizes the missing data for these analysis.