An Open-Label Extension Study of UT-15C in Subjects with Pulmonary Arterial Hypertension - A Long-Term Follow-up to Protocol TDE-PH-310

IND Number 71, 537

EudraCT Number 2012-000098-21

Protocol TDE-PH-311

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	03 February 2012
Amendment 01	14 March 2012
Amendment 02	13 June 2012
Amendment 03	05 December 2012
Amendment 04	10 March 2014
Amendment 05	09 January 2015
Amendment 06	29 September 2016
Amendment 07	13 July 2018

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "An Open-Label Extension Study of UT-15C in Subjects with Pulmonary Arterial Hypertension - A Long-Term Follow-up to Protocol TDE-PH-310" Amendment 7 dated 13 July 2018 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 (FDA) 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 Corp.

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice daily
C_{max}	Maximum Plasma Concentration
CTD	Connective Tissue Disease
CVD	Cardiovascular Disease
CYP	Cytochrome P450
eCRF	Electronic Case Report Form
EC	Ethics Committee
ERA	Endothelin Receptor Antagonist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
H-L	Hodges-Lehmann
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional/Independent Review Board
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
NTP	National Toxicology Program
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PDE5-I	Phosphodiesterase-5 Inhibitor
PGI_2	Prostacyclin
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
sGC	Soluble Guanylate Cyclase Stimulator
TID	3 Times Daily
UT-15C	Treprostinil Diethanolamine
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

PROTOCOL SYNOPSIS

Title	Open-Label Extension Study of UT-15C in Subjects with Pulmonary Arterial Hypertension - A Long-Term Follow-up to Protocol TDE-PH-310
Study Phase	III
Indication	Pulmonary Arterial Hypertension (PAH)
Primary Objective	• To provide UT-15C for eligible subjects who participated in Study Protocol TDE-PH-310
Secondary Objective(s)	• To assess the long-term safety of oral UT-15C • To assess the effect of continued long-term therapy with UT-15C on exercise capacity (6-Minute Walk Distance [6MWD]/Borg dyspnea score), World Health Organization (WHO) Functional Class, and N-terminal pro-brain natriuretic peptide (NT-proBNP) (at Week 48 only)
Exploratory Objective	• Optional evaluation of pharmacogenomics
Study Design	Multi-center, open-label study for eligible patients who participated in TDE-PH-310
Sample Size	Up to 850 subjects from Protocol TDE-PH-310 will be enrolled.
Summary of Subject Eligibility Criteria	Participation and completion of required visits from TDE-PH-310. Discontinued due to clinical worsening in TDE-PH-310. All ongoing subjects at the time the number of adjudicated clinical worsening (morbidity or mortality) events specified in Protocol TDE-PH-310 has occurred will be eligible to participate in this open-label study.
Drug Dosage and Formulation	All subjects will receive oral treprostinil diethanolamine (UT-15C) sustained release tablets. Study drug will be provided in 0.125, 0.25, 0.5, 1.0, and 2.5 mg sustained-release (SR) tablets to be administered 3 times daily (TID) immediately after (~10 minutes) consuming food. For subjects who were randomly allocated to UT-15C in TDE-PH-310, the initial dose of UT-15C in the open-label study will be based upon their final dose in TDE-PH-310. Dose escalation of UT-15C may occur in either 0.125 or 0.25 mg increments no more than every 24 hours based on adverse effects and signs and symptoms of PAH. For subjects who were randomly allocated to placebo in Protocol TDE-PH-310, dosing of UT-15C will be initiated at 0.125 mg TID. Dose escalations can occur no more than every 24 hours (3 consecutive doses) in 0.125 mg increments TID during the first 4 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 every 24 hours. There is no maximum dose specified for this study. Note that sudden dose escalations or reductions may lead to intolerable adverse effects or worsening PAH and gradual dose titrations are recommended to reduce the risk to subjects.
Control Group	None
Route of Administration	Oral
Procedures	Study visits will occur at Baseline, Weeks 6, 12, and every 12 weeks thereafter. Study visits will continue until either UT-15C becomes commercially available within the respective territories, or the study is discontinued by the Sponsor. Study assessments will include: • 6-Minute Walk Test (6MWT)/Borg dyspnea score • WHO Functional Class • NT-proBNP (Week 48 only) • Safety (vital signs, adverse events [AEs], clinical laboratory parameters, concomitant medications) • Optional assessment of pharmacogenomics.
Statistical Considerations	All data will be summarized in tables and listings.
Sponsor	United Therapeutics Corp. 55 T. W. Alexander Drive 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 (CTD), portal hypertension, infection with the human immunodeficiency virus (HIV), a history of cocaine inhalation, or 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 3 major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis. There are a number of metabolic pathways which contribute to these changes that involve vasoactive mediators such as the vasodilators nitric oxide and prostacyclin, 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 prostacyclin (epoprostenol sodium or Flolan®, Veletri®); (2) the prostacyclin (PGI_2) analogues, subcutaneous (SC), intravenous (IV), and inhaled treprostinil (Remodulin®, Tyvaso®), oral treprostinil diethanolamine (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 (ERAs), bosentan (Tracleer®), ambrisentan (Letairis®, Volibris®), and macitentan (Opsumit®), and (5) a soluble guanylate cyclase stimulator (sGC), riociguat (Adempas®).

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 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 prostacyclins 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 (eg, 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 prostacyclin 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 5,000 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 Sprague Dawley 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. F_0 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 6 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 2 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 20 weeks and 2 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 beagle dogs was also 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 1 group of 4 telemetered male dogs. Preliminary data support that oral administration of diethanolamine at doses up to 2 mg/kg/dose twice daily (BID) (4 mg/kg/day) to male 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 (AEs) associated with Remodulin in clinical trials of patients with PAH were related to the pharmacological properties of Remodulin and were generally not serious. These prostacyclin-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, over 17,000 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 1–3 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 3 times daily dosing (TID) in the ongoing Phase 1–3 development program. The average exposure is approximately 2 years; the longest exposure is almost 7 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) 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.

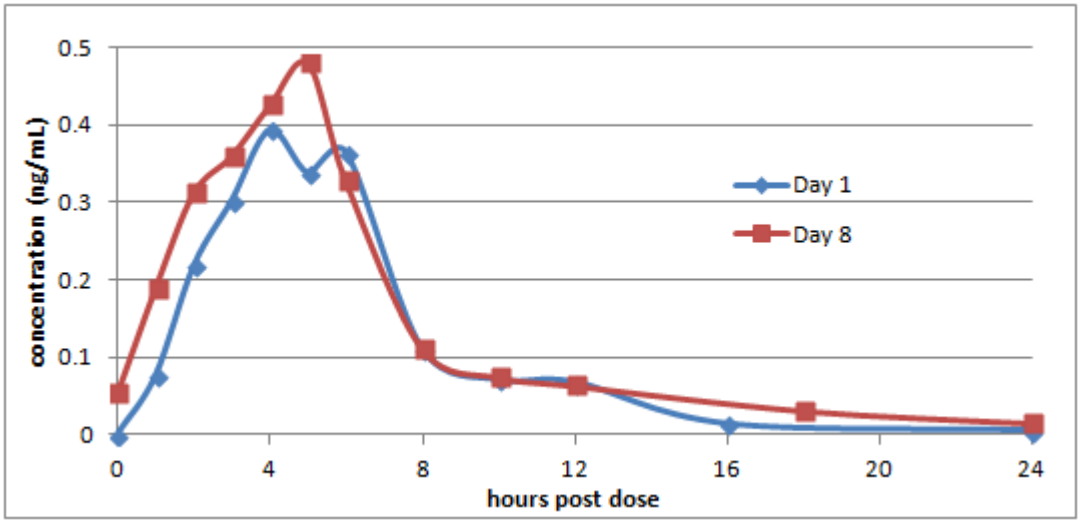
To date, the majority of UT-15C studies have been conducted with BID dosing. In an attempt to understand the pharmacokinetics of TID a study was conducted in healthy volunteers. In this open-label, single-center study 19 healthy subjects received 0.5 mg TID for 7 days. On the morning of Day 1 subjects received a single 0.5 mg dose, on Day 2 to Day 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 pharmacokinetic sampling occurred following the 8AM doses on Days 1, 7, and 8. Trough samples were collected prior to the morning (8AM) and evening (8PM) doses on Days 4, 5, and 6.

Nineteen subjects (9 Females:10 Males) with a mean age of 35.2 years (range: 20 to 54 years) were enrolled. On Day 1 the mean (±standard deviation [SD]) maximum plasma

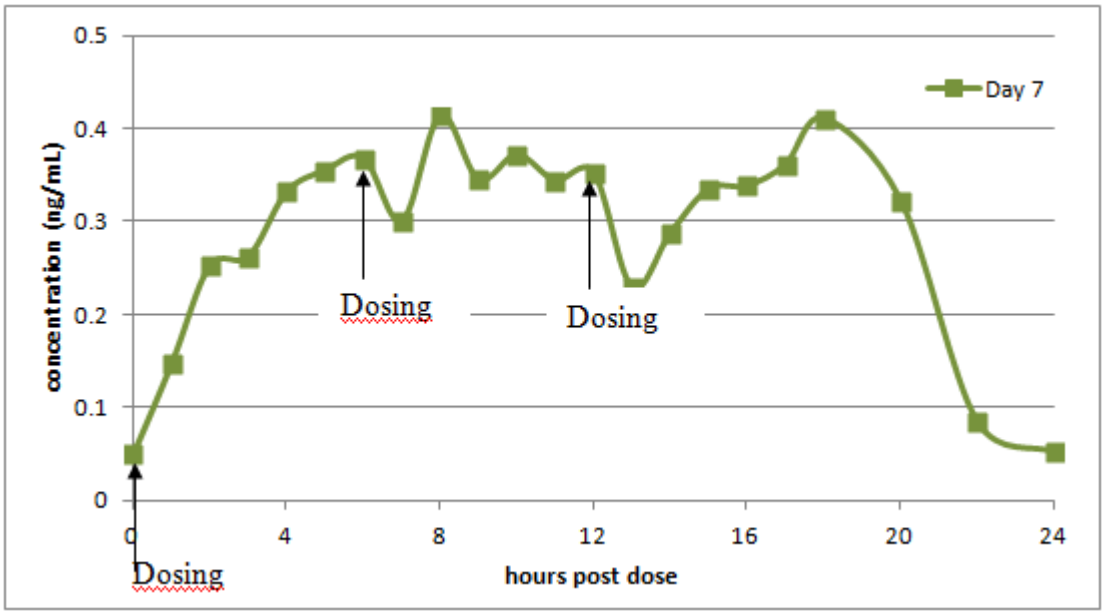
concentration (C_{max}) of treprostinil was 0.574±0.22 ng/mL, occurring at a median time of 4 hours (range: 2 to 6 hours). In comparison, the Day 8 mean (±SD) C_{max} was 0.615±0.32 ng/mL, occurring at a median time of 4 hours (range: 1 to 6 hours) (See Figure 1).

Figure 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 hours) following the morning dose (Figure 2). This indicates that maximum plasma concentration during a daily interval at steady state occurs after the evening (or third) dose of the day.

Figure 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 7 subjects and primarily included known prostacyclin class-effect related AEs (eg, 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 3 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 1,000 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 800 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.

A total of 354 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 3 (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 3 deaths in each of the treatment groups.

The Hodges-Lehmann (H-L) estimate of 6MWD 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 0.25 mg and 0.5 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 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 2 (33%) and Class 3 (66%) of varied etiologies, including idiopathic or heritable PAH (75%), cardiovascular disease (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.

Adverse Events 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 prostacyclin 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 (eg, 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.

A total of 310 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 of age (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 3 (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 N-terminal proBNP (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 studies 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. Adverse Events were typical of prostacyclin

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 DISEASE/CONDITION

Prostacyclin is a potent endogenous vasodilator and inhibitor of platelet aggregation. A synthetic salt of prostacyclin (ie, 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 IV delivery. Treprostinil sodium is a chemically stable, longer acting analogue that has shown clinical effectiveness when administered by SC, IV (Remodulin, Remodulin Package Insert 2014], or inhaled routes (Tyvaso, Tyvaso Package Insert 2017).

Parenteral prostacyclins 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 treatment with an approved oral monotherapy to allow patients to benefit from the simplicity of an oral dosage form.

An innovative salt form, treprostinil diethanolamine, has been developed to deliver prostacyclin 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 that combination therapy, particularly with a prostacyclin, may prevent or delay the progression of the disease and thereby prolong the time to clinical worsening.

1.4 CLINICAL HYPOTHESIS

This open-label study will evaluate the safety of continued therapy with UT-15C in subjects who have completed TDE-PH-310. This study will provide long-term, open-label data regarding the safety and efficacy of UT-15C for the treatment of PAH.

The hypothesis for the frequency of dosing change 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 reduces the occurrence of prostacyclin 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 and improving exercise capacity at Week 24.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to provide UT-15C SR tablets for eligible subjects who participated in TDE-PH-310.

2.2 SECONDARY OBJECTIVES

Secondary objectives of this study are:

- To assess the long-term safety of UT-15C
- To assess the effect of continued long-term therapy with UT-15C on exercise capacity (6MWD/Borg dyspnea score), WHO Functional Class, and plasma concentrations of NT-proBNP (Week 48 only)

2.3 EXPLORATORY OBJECTIVE

Optional evaluation of pharmacogenomics

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is an open-label study. Subject visits will occur at Baseline, Weeks 6 and 12, and every 12 weeks thereafter. The study will continue until either oral UT-15C becomes available within the respective territories or the study is discontinued by the Sponsor.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Study Timeline	Baseline[b] (Study Entry)	Week 6[c]	Week 12[c]	Follow-up Visits (every 12 weeks)[c]	Study Termination Visit[k]
Informed consent	X				
Inclusion/exclusion criteria	X				
Vital signs [a]	X	X	X	X	X
Physical examination	X				X
6MWT / Borg dyspnea score[d]	X	X	X	X	X
WHO Functional Class	X	X	X	X	X
Clinical laboratory assessments	X		X	X[e]	X
Urine pregnancy test [f]	X	X	X	X	X
Dose titration	X	X	X	X	
NT-proBNP	X			X[g]	
Drug accountability/ Compliance	X	X	X	X	X
AEs	X[h]	X	X	X	X[i]
Concomitant medications	X	X	X	X	X
Phone calls [j]	X	X	X	X	X
Pharmacogenomic Sample (Optional)				X[l]	X[l]

Abbreviations: 6MWT, 6-Minute Walk Test; AE, adverse event; NT-proBNP, N-Terminal pro-brain natriuretic peptide; WHO, World Health Organization

[a] Vital signs should be conducted following at least 5 minutes of rest and prior to or at least 30 minutes following the corresponding 6MWT.

[b] Baseline/study entry assessments (6MWT/Borg dyspnea score, WHO Functional Class, clinical laboratory parameters, NT-proBNP, vitals, and physical examination) for this study are those collected at the Study Termination Visit from Study TDE-PH-310 and prior to initiation of open-label study drug. Informed consent and inclusion/exclusion criteria are exclusive to this Protocol.

[c] Visit windows are ±14 days.

[d] 6MWT must be conducted 3 to6 hours after the last dose of UT-15C. Subject should rest for 5 minutes prior to each 6MWT.

[e] During the follow-up visits, clinical laboratory samples should be collected at the first Follow-up Visit and every other Follow-up Visit thereafter.

[f] If applicable, for women of child-bearing potential (WOCBP).

[g] NT-proBNP should only be collected at the Follow-up Visit # 3 (Week 48).

[h] Any AEs that are ongoing at the Study Termination Visit from Study TDE-PH-310 should be recorded as continuing AEs in this open-label study.

[i] Any AEs that are ongoing at the Study Termination Visit from Study TDE-PH-311 should be followed for up to 30 days after completion of the Study Termination Visit.

[j] Phone calls to the subject should occur at least weekly for the first 12 weeks, and at least monthly thereafter

[k] After the Study Termination Visit is completed, subjects should down titrate the study drug over an appropriate period of time in accordance with their clinical condition. Once the study drug has been discontinued, any remaining supplies should be returned to the clinic for drug accountability.

[l] For subjects consenting to the optional pharmacogenomic sample. The sample should be collected at the next scheduled Follow-up Visit when clinical labs are also collected. If the subject discontinues prior to the next Follow-up Visit, pharmacogenomic samples should be collected at the Study Termination Visit.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 Six-Minute Walk Test

A 6MWT (described in Appendix 15.1) will be conducted at Baseline as part of Study Termination assessments from Protocol TDE-PH-310, Week 6 and Week 12, every 12 weeks thereafter, and at the Study Termination Visit. Before each 6MWT, the subject should rest (seated) for at least 5 minutes. The 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements outlined in Section 15.1. The 6MWT should be conducted approximately 3 to 6 hours after the last dose of UT-15C.

3.3.1.2 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 (Appendix 15.1). Scores range from 0 (for the best condition) to 10 (for the worst condition).

3.3.1.3 WHO Functional Class

The WHO Functional Class for PAH (Appendix 15.2) will be assessed at Baseline as part of Study Termination assessments from Protocol TDE-PH-310, Week 6, Week 12, every 12 weeks thereafter, and at the Study Termination Visit.

3.3.1.4 N-terminal proBNP

Plasma NT-proBNP concentration is a useful biomarker for PAH as it is associated with changes in right heart morphology and function (Fijalkowska 2006). The NT-proBNP sample collection will occur at Baseline as part of Study Termination assessments from Protocol TDE-PH-310 and at Follow-up Visit #3 (Week 48) only.

3.3.1.5 Optional Pharmacogenomics

For subjects consenting to pharmacogenomic analysis, blood samples will be collected at the first possible Follow-up Visit when clinical labs are also collected. If the subject discontinues prior to their next Follow--up Visit, pharmacogenomic samples will be collected at the Study Termination Visit. Pharmacogenomic samples will be shipped to the central laboratory for processing and storage prior to analysis. Genetic variants will be analyzed to evaluate their

association with observed clinical response during the blinded Study TDE-PH-310 and tolerability to prostacyclin therapy. Subjects who do not wish to participate in the optional pharmacogenomic research may still participate in the clinical study.

3.3.2 Safety

3.3.2.1 Vital Signs

Vital signs will be assessed at Baseline as part of Study Termination assessments from Protocol TDE-PH-310 and at all subsequent protocol-required visits. 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. Vital signs must be collected following at least 5 minutes of rest to ensure accurate measurement.

3.3.2.2 Physical Examination

A physical examination will be assessed at Baseline as part of Study Termination assessments from Protocol TDE-PH-310 and at the Study Termination Visit.

3.3.2.3 Clinical Laboratory Assessments

Clinical laboratory parameters will be assessed at Baseline/Study Entry as part of Study Termination assessments from Protocol TDE-PH-310. Clinical laboratory assessments will also be assessed at Week 12, at every other Follow-up Visits thereafter, and at the Study Termination Visit. Clinical laboratory parameters to be assessed at the study visits are listed in Appendix 15.4. A urine pregnancy test will be collected at every visit for women of childbearing potential (WOCBP).

3.3.2.4 Adverse Event Assessments

Any AEs that are ongoing at the Study Termination Visit from Study TDE-PH-310 should be recorded as continuing AEs in this open-label study. Section 9 and Appendix 15.4 provide the guidelines and definitions for recording AEs.

All AEs will be captured from the time the informed consent form (ICF) is signed. All AEs should be followed until 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 serious adverse events (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 Appendix 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.

3.3.2.5 Concomitant Medications

Concomitant medication may be adjusted as deemed clinically necessary by the Investigator during the study. However, additional prostanoid therapies should not be permanently added. Concomitant medications used during the study will be reviewed at each protocol-required visit and recorded as they are prescribed in the Electronic Case Report Form (eCRF). Concomitant medications that were ongoing at the end of the TDE-PH-310 Study will be recorded in the eCRF for the open-label study.

3.4 NUMBER OF CENTERS

The centers who participate in Study TDE-PH-310 (approximately 150) will take part in the study.

3.5 NUMBER OF SUBJECTS

Up to 850 subjects from TDE-PH-310 may be eligible to participate in the study.

3.6 ESTIMATED STUDY DURATION

The study will continue for approximately 6 years. The study may be discontinued at any time if, in the opinion of the Investigators 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. Subjects that discontinue the study will be contacted approximately 30 days (±5 days) after study drug discontinuation to confirm their survival status. Subjects may also continue to be

contacted after the final study visit to assess AEs/SAEs (see Section 9.2 for additional details).

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

A subject is eligible to participate in this study if all of the following criteria apply:

1. The subject voluntarily provides informed consent to participate in the study.
2. The subject participated in Study TDE-PH-310 and met the definition of clinical worsening (as specified in Protocol TDE-PH-310), remained on study drug, was compliant with study procedures and assessments during the TDE-PH-310 Study or was currently enrolled in that study at the time the study was discontinued by the Sponsor.
3. All WOCBP must practice true abstinence from intercourse when it is in line with their preferred and usual lifestyle, or use 2 different forms of highly effective contraception for the duration of the study, and for at least 30 days after discontinuing study medication. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device, or (4) partner vasectomy. For women of childbearing potential, a negative urine pregnancy test is required at Baseline (study entry) prior to initiating study medication. 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).
4. Males participating in the study must use a condom during the length of the study, and for at least 48 hours after their last dose of study medication.

4.2 EXCLUSION CRITERIA

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

1. The subject is pregnant or lactating.
2. The subject has received infused or inhaled prostacyclin therapy for 29 days or more.
3. The subject was prematurely discontinued from Study TDE-PH-310 for reasons other than a clinical worsening event.
4. The subject developed a concurrent illness or condition during the conduct of TDE-PH-310 which, in the opinion of the Investigator, would represent a risk to overall health if they enrolled in this study.

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

In this open-label study, there are no restrictions on concomitant medications, including the approved PAH therapies, with the exception of the permanent addition (29 days or more) of prostacyclin or prostacyclin analogue therapy. Subjects who receive permanent prostacyclin or prostacyclin analogue therapy must discontinue this open-label study.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

All subjects will receive UT-15C SR tablets during this open-label study. Subjects will retain the same subject number as assigned for the TDE-PH-310 study.

5.2 RANDOMIZATION

This study is not randomized.

5.3 BLINDING

This study is not blinded.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

The UT-15C tablets are sustained release osmotic tablets. UT-15C tablets are provided as 0.125, 0.25, 0.5, 1.0, and 2.5 mg tablet strengths. The 0.125, 0.25, 0.5, 1.0, 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.

For subjects who were randomly allocated to receive placebo in TDE-PH-310, dosing of UT-15C will be initiated and optimized as in the previous protocol, including all safety monitoring and periodic telephone contacts. That is, the first dose of UT-15C (0.125 mg) should be taken by the subject at the site immediately after (approximately 10 minutes) consuming food. Oral dosing of study drug will be continued at 0.125 mg TID (every 6 to 8 hours) immediately after (approximately 10 minutes) consuming food. Subjects must be instructed to take the appropriate amount of UT-15C tablets based upon their prescribed dose. For the first 4 weeks, each dose of study drug should be adjusted in 0.125 mg increments no

more than every 24 hours as clinically indicated. Following 4 weeks of treatment, each dose of study drug may be adjusted in 0.125 or 0.25 mg increments every 24 hours as clinically indicated. Doses of UT-15C should continue to be increased in the absence of dose-limiting drug-related adverse effects, to ensure the subject receives the optimal clinical dose throughout the study. There is no maximum dose of UT-15C in this open-label study.

Subjects who were randomly allocated to receive UT-15C in TDE-PH-310 will begin the open-label study at the same dose they were receiving at the Study Termination Visit in TDE-PH-310, and subsequent adjustments will be made based on symptoms of PAH and adverse effects.

All subjects must be instructed to take the appropriate amount of 0.125, 0.25, 0.5, 1.0 and/or 2.5 mg tablets based upon their prescribed dose. All dose changes should be conducted under appropriate medical supervision in consultation with the study site. At least weekly telephone calls between site personnel and the subject should be made during the first 12 weeks of the study to monitor AEs and make decisions about dose titration. After Week 12, at least monthly telephone calls should be made to continue to monitor AEs and make decisions regarding appropriate dose titrations. If dose titration is considered appropriate, site personnel will instruct the subject to modify their dose and the dose change will be recorded in source documentation. If it becomes necessary for a subject to modify their dose of UT-15C (eg, 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.

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 or 0.25 mg increments every 12 to 24 hours. Larger dose reductions may be necessary in the event of an emergency situation.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

This study is not blinded.

6.3 COMPLIANCE

The Principal Investigator or other site personnel under the direction of the Principal Investigator will be responsible for dose titration of UT-15C and recording all dosing information in source documents. During telephone calls, site personnel will record the current dosing regimen of UT-15C and determine if the subject is taking UT-15C as prescribed.

At scheduled study visits, subjects should be instructed to bring all study drug (including empty and unused bottles) to the investigational site. Upon return of study drug at each required protocol visits (eg, Weeks 6, 12, 24, etc), 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 noncompliance 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 (eg, Weeks 6, 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 at unscheduled visits.

7 EXPERIMENTAL PROCEDURES

7.1 TREATMENT PHASE

7.1.1 Baseline/Study Entry

All data collected at the subject's Study Termination Visit during TDE-PH-310 and prior to initiating open-label study drug will serve as Baseline/Study Entry assessments for this study. Following completion of the Study Termination assessments for a subject and entry of required data into the interactive voice or web response system (IVRS/IWRS), the site

personnel will be unblinded to that subject's treatment assignment. Subjects must sign an ICF and meet inclusion/exclusion criteria specific to this protocol. The recommended sequence of events for Baseline/Study Entry is displayed below:

- Informed consent (prior to any study assessments)
- Inclusion/exclusion criteria
- Vital signs (following at least 5 minutes of rest)*
- Physical examination*
- WHO Functional Class*
- AE assessment*
- 6MWT/Borg dyspnea score (for subjects randomized to UT-15C in TDE-PH-310, the 6MWT to be initiated 3 to 6 hours after the last dose of UT-15C; 6MWT to be conducted following at least 5 minutes of rest; Borg dyspnea score to be conducted immediately following 6MWT)*
- Urine pregnancy test (for WOCBP)*
- Clinical laboratory assessments*
- Plasma NT-proBNP*
- Study drug dosing (for subjects randomized to placebo in TDE-PH-310, the initial dose of UT-15C in TDE-PH-311 should be taken at the study site)
- Drug accountability
- Concomitant medications*
- Weekly telephone calls are highly recommended especially after any dose changes

**assessments conducted during the Study Termination Visit for the TDE-PH-310 study will not need to be repeated*

The AEs that were ongoing at the end of the TDE-PH-310 study will be recorded as ongoing events for this open-label study. Concomitant medications that were ongoing at the TDE-PH-310 Study Termination Visit will be recorded in the eCRF for the open-label study. Once the subject signs the ICF for this study, all ongoing AEs must be recorded and documented on the eCRF. All AEs and concomitant medications will be reported continuously for the duration of the study. Phone calls to the subject must begin within 1 week of the subject receiving the first dose of study drug and continue to be made weekly for the first 12 weeks of the study. After the first 12 weeks, phone calls must be made at least monthly. Dose titration should occur as needed in accordance with Section 6.1.

7.1.2 Week 6 Visit

Subjects are to return to the study site at Week 6. This visit should be conducted within 14 days of the scheduled visit (as determined by the Baseline/Study Entry Visit) and the following assessments are to occur in the order recommended below:

- Vital signs (following at least 5 minutes of rest)
- WHO Functional Class
- AE assessment
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the last dose of UT-15C; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- UT-15C dose titration
- Drug accountability/compliance
- Concomitant medications
- Weekly telephone calls are highly recommended, especially after any dose changes

7.1.3 Week 12 Visit

Subjects are to return to the study site at Week 12. This visit should be conducted within 14 days of the scheduled visit (as determined by the Baseline/Study Entry Visit) and the following assessments are to occur in the order recommended below:

- Vital signs (following at least 5 minutes of rest)
- WHO Functional Class
- AE assessment
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the last dose of UT-15C; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- Clinical laboratory assessments
- UT-15C dose titration
- Drug accountability/compliance
- Concomitant medications
- Monthly telephone calls are highly recommended

7.1.4 Follow-up Visits (every 12 weeks)

Subjects should return to the study site every 12 weeks after the Week 12 visit. These visits should be conducted within 14 days of the scheduled visit (as determined by the Baseline/Study Entry Visit). Assessment of AEs, concomitant medications, and dose titration should occur continuously between and during study visits. The recommended sequence of events for Follow-up Visits is displayed below:

- Vital signs (following at least 5 minutes of rest)
- WHO Functional Class
- AE assessment
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the last dose of UT-15C; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- Clinical laboratory assessments*
- Plasma NT-proBNP**
- UT-15C dose titration
- Drug accountability/compliance
- Concomitant medications
- Monthly telephone calls are highly recommended
- Collection of blood sample for evaluation of pharmacogenomics (optional) ***

**to be assessed at the first Follow-up Visit and every other visit thereafter*
***to be assessed at the third Follow-up Visit only (Week 48)*
**** The sample should be collected at the next scheduled Follow-up Visit when clinical labs are also collected. Subjects must sign an informed consent prior to sample collection.*

7.1.5 Study Termination Visit

When subjects discontinue the study, they will complete a Study Termination Visit. If possible, each subject should remain on study drug until they have completed the Study Termination visit. After the Study Termination Visit is completed, subjects should down titrate the study drug over an appropriate period of time in accordance with their clinical condition. Once the study drug has been discontinued, any remaining study drug should be returned to the clinic for drug accountability. The following assessments will take place at the Study Termination visit:

- Vital signs (following at least 5 minutes of rest)
- Physical examination
- WHO Functional Class
- AE assessment (for AEs ongoing at the Study Termination Visit, assessments to continue for up to 30 days beyond the Study Termination Visit)
- 6MWT/Borg dyspnea score (if possible, the 6MWT is to be initiated 3 to 6 hours after the last dose of UT-15C; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- Clinical laboratory assessments
- Drug accountability/compliance
- Concomitant medications
- Collection of blood sample for evaluation of pharmacogenomics (optional) *****

***** *If a subject discontinues prior to their next Follow-up Visit, pharmacogenomic samples will be collected at the Study Termination Visit.*

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 deviated from the protocol
- The subject's behavior is likely to undermine the validity of his/her results
- The subject becomes pregnant

When a subject is discontinued from the study, the Investigator will complete the Study Termination record and provide an explanation, if needed. If UT-15C has been administered, the Investigator should make every effort to perform all Study Termination evaluations following termination of UT-15C treatment but prior to discharge from the study.

8.2 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of the Investigator and/or Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include,

but is not limited to, the presence of serious, life-threatening, or fatal AEs, or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.3 CRITERIA FOR DISCONTINUING THE SITE

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

- The Principal Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the site
- International Council for Harmonisation (ICH) Good Clinical Practice (GCP) or 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 study 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.

9.1.3 Adverse events associated with progression of PAH

Expected AEs that may be related to the progression of a subject's PAH are defined in Appendix 15.5. 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, each event must be recorded as an AE/SAE in the eCRF, if it meets 1 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

All AEs will be captured from the time the ICF is signed. Any AEs that are ongoing at the Study Termination Visit from Study TDE-PH-310 should be recorded as continuing AEs in this open-label study. An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the eCRF (see Appendix 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 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 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.

9.3 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 (+ 1 919-313-1297 [U.S./Japan] or + 44 1932 573 888 [Europe/ROW]) or email (drugsafety@unither.com). A completed SAE report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corp. A follow-up SAE report form must be forwarded to Global Drug Safety at United Therapeutics Corp. 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 emailing this form to Global Drug Safety at United Therapeutics Corp. (+ 1 919-313-1297 [U.S./Japan] or + 44 1932 573 888 [Europe/ROW]) or drugsafety@unither.com). Subjects who become pregnant during the study will be withdrawn

from active participation in the study and will discontinue study drug after an appropriate period of down-titration.

United Therapeutics Global Drug Safety Department will follow up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to request that the Investigator 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, IRBs, and/or 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's data into the eCRF. Data for any subject who signs an informed consent form 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

No formal sample size calculation has been conducted. All eligible subjects from TDE-PH-310 may enter this study.

10.3 ANALYSIS PLAN

All safety and efficacy data will be summarized in tables and listings and analyzed for trends over time. No formal hypothesis testing is planned.

The safety population will be defined as all subjects in the study that received UT-15C at any time during the course of the study. Safety analyses will be performed on the safety population. All AEs as recorded by the Investigators will be assigned MedDRA preferred terms by the Sponsor for reporting purposes.

10.4 OTHER ANALYSES

Pharmacogenomic samples will be evaluated for genetic variants. Other exploratory analyses may be conducted based on available study data.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics Corp. will supply UT-15C for administration during the study. UT-15C tablets will be provided as 0.125, 0.25, 0.5, 1, and 2.5 mg strengths for 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). 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 will be provided in child resistant bottles each containing 100 tablets, or in other appropriate packaging configurations as may be required.

11.2 LABELING

Each bottle will be labeled in accordance with applicable national regulations, to include at least the following information: study drug, study 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 CLINICAL TRIAL MATERIAL

All study drug will be stored at room temperature (up to 25°C with brief excursions to 30°C permitted). 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 bottle assigned to the subject at each study visit 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 CLINICAL TRIAL MATERIAL

Study sites will be supplied with a sufficient quantity of UT-15C to begin enrollment in the study. An IVRS/IWRS will be utilized to manage resupply with respect to each subject's visit schedule. If required, additional study drug may be dispensed to a subject between protocol-required visits. At each protocol required visit, all study drug dispensed to the subject should be returned to the study site (including empty and unopened bottles). A new supply of study drug will be dispensed at each protocol-required visit.

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 OR APPLICABLE 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 informed consent form and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/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 study, the following documents (at minimum) will be provided to the site: Investigator's Brochure, Protocol, ICF, Budget Agreement, and access to an eCRF.

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

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corp., 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 Corp. 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, the study records should be maintained for at least 15 years after study discontinuation. The Investigator must notify United Therapeutics Corp. 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 Corp. 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 Corp. or its designee may periodically contact the site and conduct on-site visits.

14 REFERENCES

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15 APPENDICES

15.1 PROCEDURE FOR SIX MINUTE WALK EXERCISE TEST AND BORG DYSPNEA SCORE

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 meters in length (but no shorter than 15 meters [16 yards or 50 feet] in length at minimum) and at least 2 to 3 meters 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 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you

possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

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

"Do you have any questions about the test?"
"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 CLASS FOR PAH

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	
Albumin	White Blood Cell Count (no differential)	
Blood Urea Nitrogen/Urea		
Total Bilirubin		
Indirect Bilirubin		
Direct Bilirubin		
Alkaline Phosphatase		
Alanine Aminotransferase (ALT)		
Aspartate Aminotransferase (AST)		
Gamma-glutamyl transferase (GGT)		
Creatinine		

Visit Test Schedule

Visit	Labs Collected
Baseline/Study Entry****	Chemistries, Hematology, NT-proBNP, urine dipstick, urine pregnancy***
Week 6 Visit	Urine pregnancy***
Week 12 Visit	Chemistries, Hematology, urine pregnancy***
Follow-up Visits*****	Chemistries, Hematology, NT-proBNP*, urine pregnancy***
Study Termination Visit	Chemistries, Hematology, urine dipstick, urine pregnancy***

* NT-proBNP collected at Baseline/Study Entry and Follow-up Visit (Week 48) only
** pH, specific gravity, presence of protein or blood
*** For women of childbearing potential (WOCBP)
**** Baseline/Study Entry clinical laboratory assessments for this study are those collected at the last visit (Study Termination) from study TDE-PH-310 and prior to initiation of open-label UT-15C.
***** During Follow-up Visits, clinical laboratory samples should be collected at the first Follow-up Visit and every other Follow-up Visit thereafter.

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 SAE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization, is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE 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 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)