Protocol TDE-PH-304

An Open-Label Extension Trial of UT-15C SR in Subjects with Pulmonary Arterial Hypertension

IND# 71,537

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CONFIDENTIAL

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Confidentiality Statement:

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INVESTIGATOR AGREEMENT

I have read the attached protocol entitled “An Open-Label Extension Trial of UT-15C SR in Subjects with Pulmonary Arterial Hypertension”, Amendment 5 dated 20 March 2013 and agree to abide by all provisions set forth therein. This protocol has been received for information only and must not be implemented before all necessary regulatory agency and ethics approval documents have been obtained.

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

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

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

_____ _____
Signature of Principal Investigator Date

_____
Printed Name of Principal Investigator

PROTOCOL SUMMARY

Protocol Number:	TDE-PH-304
Protocol Title:	An Open-Label Extension Trial of UT-15C SR in Subjects with Pulmonary Arterial Hypertension
Study Phase:	3
Name of Drug:	UT-15C SR (treprostinil diethanolamine)
Indication:	Pulmonary Arterial Hypertension (PAH)
Study Objectives:	To provide, or continue to provide, UT-15C SR for eligible subjects who participated in protocols TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308, or any additional UT-15C SR clinical protocols evaluating subjects with PAH. To assess the long-term safety of UT-15C SR in these subjects through assessment of adverse events and laboratory parameters. To assess the effect of continued therapy with UT-15C SR on exercise capacity after one year of treatment.
Study Design:	This is a multi-center, open-label study for eligible patients who participated in Protocol TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308, or any additional UT-15C SR clinical protocols evaluating subjects with PAH.
Sample Size:	Approximately 900 subjects from protocols TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, and TDE-PH-308 plus additional subjects from any additional UT-15C SR clinical protocols evaluating subjects with PAH.
Summary of Subject Eligibility Criteria:	Participation in study TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308 or any additional UT-15C SR clinical protocol is required. Subjects must complete all assessments in one of these studies to be eligible.
Drug Dosage and Formulation:	UT-15C Sustained Release Tablets will be provided as 0.25, 0.5, 1, and 2.5 mg tablet strengths. UT-15C SR tablets may also be provided as a 0.125 mg strength, if available. For subjects on placebo at the end of the TDE-PH-301, TDE-PH-302, and TDE-PH-308 protocols, treatment will be initiated at 0.25 mg twice daily (every 12 hours +/- 1 hour) with dose escalation of an additional 0.25 to 0.5 mg twice daily every 3 days if clinically indicated based upon adverse events and signs and symptoms of PAH. The 0.125 mg strength, if available, may be used throughout the study if a 0.25 mg dose increase is not tolerated and an intermediate dose is required. Doses should be optimized throughout the study. For subjects on active therapy in TDE-PH-202, TDE-PH-203, TDE-PH-205 TDE-PH-301, TDE-PH-302, and TDE-PH-308 the initial dose of the open-label study will be

	based upon their ending dose in the previous study, and dose modification will be based on adverse events and signs and symptoms of PAH. Twice daily(BID) dosing should occur (every 12 hours +/- 1 hour) with dose escalation of an additional 0.25 to 0.5 mg twice daily every 3 days if clinically indicated based upon adverse events and signs and symptoms of PAH. Three times (TID) daily dosing for subjects enrolled from the TDE-PH-205 study or those subjects transitioning from BID to TID dosing, study drug should be taken every 6-8 hours with dose escalation of an additional 0.125 to 0.25 mg twice daily every 3 days if clinically indicated based upon adverse events and signs and symptoms of PAH. All study drug should be administered immediately following (~10 minutes) breakfast and dinner for BID dosing and with food for TID dosing.
Route of Administration:	Oral
Study Visit Schedule:	Study visits will be timed to occur 3, 6, 12, 24, 36 months after each subject's first exposure to UT-15C SR. The study will continue with yearly visits beyond 36 months until either UT-15C SR is approved by the appropriate regulatory authorities or the study is discontinued by the sponsor. Subjects receiving placebo in the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308) and subjects enrolled from the TDE-PH-202 study who were in Dose Groups 1 or 2 and permanently discontinued treatment must be contacted weekly by telephone during the first 12 weeks of the open-label study. Subjects transitioning from BID to TID dosing should be contacted weekly for the first four weeks after transitioning. Monthly telephone calls must be conducted for all subjects actively participating in TDE-PH-304, regardless of study drug allocation (UT-15C SR or placebo) in the previous study. In addition to the scheduled study visits, all subjects must be seen in the clinic no less than once every six months for routine standard of care medical evaluation.
Efficacy Assessment:	A 6-Minute Walk Test with Borg Dyspnea Score will be conducted at the study visit occurring 1 year after the subject first received UT-15C SR.
Safety Assessments:	Adverse events and clinical laboratory parameters will be assessed throughout the study.
Statistical Considerations:	All data will be summarized in tables and listings.
Sponsor:	United Therapeutics Corporation 55 T.W. Alexander Dr. P.O. Box 14186 Research Triangle Park, NC 27709 United States of America

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice Daily
ºC	Degrees Celsius
CRF	Case Report Form
EC	Ethics Committee
ERA	Endothelin Receptor Antagonist
FDA	Food and Drug Administration
ºF	Degrees Fahrenheit
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonisation
iMTD	Individual Maximum Tolerated Dose
IRB	Independent/Institutional Review Board
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
PAH	Pulmonary Arterial Hypertension
PDE_5	Phosphodiesterase 5
PGI_2	Prostacyclin
SAE	Serious Adverse Event
SR	Sustained Release
TID	Three Times Daily
UT-15C SR	Treprostinil Diethanolamine

1 BACKGROUND AND RATIONALE

1.1 Pulmonary Arterial Hypertension: Definition of Clinical Problem

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

There are three major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the blood vessel wall, and thrombosis. There are a number of metabolic pathways implicated as contributing to these changes including vasoactive mediators such as the vasodilators nitric oxide and prostacyclin, the vasoconstrictor endothelin-1, and the phosphodiesterase type-5 mediated vasodilation. These substances affect not only vascular tone but also effect vascular remodeling and represent current pharmacologic targets.[1]

Approved pharmacotherapies for PAH include: (1) intravenous prostacyclin (epoprostenol sodium or Flolan®)[2,3], (2) the prostacyclin analogues, subcutaneous (SC), intravenous (IV), and inhaled treprostinil sodium (Remodulin®; Tyvaso®) and inhaled iloprost (Ventavis®), (3) the oral phosphodiesterase-5 inhibitors (PDE5-I), tadalafil (Adcirca®) and sildenafil (Revatio®); and (4) the oral endothelin receptor antagonists (ERA)[9, 10] , bosentan (Tracleer®) and ambrisentan (Letairis®, Volibris®).[11,12]

1.2 Treprostinil Background

1.2.1 UT-15C SR Nonclinical

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 SD rats. Mortality observed at the high dose indicates systemic exposure of animals to the test article. Based upon these findings, treprostinil diethanolamine (UT-15C) was concluded to be negative in the rat micronucleus assay.

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

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

Studies have been conducted by the United States National Toxicology Program (NTP) to determine whether diethanolamine by itself (without treprostinil or any other drug) causes cancer. Two years of topical administration of diethanolamine to mice produced an increased incidence (compared to a control group) of malignant liver tumors in males and females, as well as an increased incidence of malignant kidney tumors in males. Doses used in this study were approximately 720 to 2,900 times higher (based on mg/m^2 dosing) than the proposed starting doses for the UT-15C clinical studies. However, in transgenic mice and rats, topical administration of diethanolamine for twenty weeks and two years, respectively, was not associated with the development of any cancers. The relevance of the mouse tumor findings to humans is currently unknown. Diethanolamine is listed on the FDA database of inactive ingredients for a number of approved drug products with no apparent safety concerns.

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

1.2.2 UT-15C SR 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 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, well over 10,000 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.

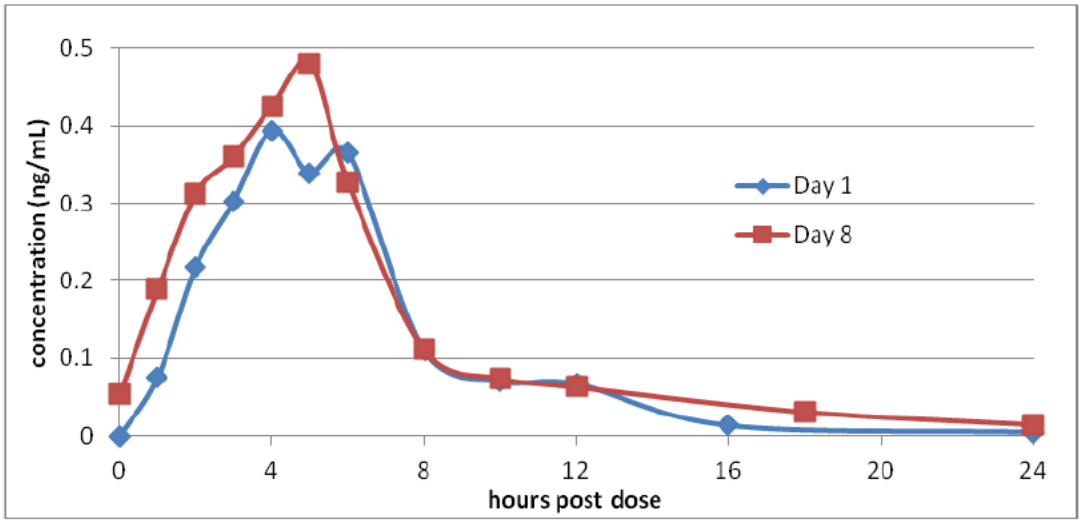
UT-15C has been administered to approximately 1,600 subjects in phase I-III clinical trials. UT-15C doses of up to 3 mg twice daily (BID) have been administered to healthy volunteers and patients with PAH have received up to 22 mg BID in the ongoing phase III development program. The longest individual exposure is now greater than five years.

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

To date, the majority of UT-15C clinical studies have been conducted with twice daily dosing. In an attempt to understand the pharmacokinetics of three times daily dosing (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 Days 2-7 the subjects received TID dosing of 0.5 mg (approximately 8AM, 2PM, and 8PM) administered immediately following a meal. On the morning of Day 8, the subjects received a final dose of 0.5 mg.

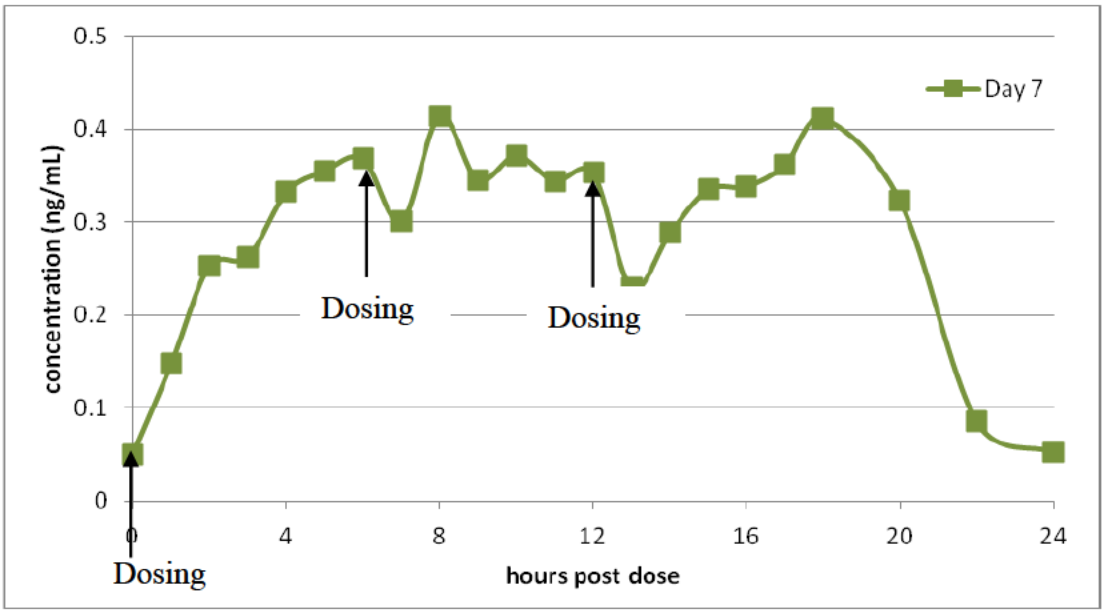
Intensive 24 hour PK sampling occurred following the 8AM doses on Days 1, 7 and 8. Trough samples were collected prior to the morning (8 AM) and evening (8PM) doses on Days 4, 5 and 6.
Nineteen subjects (9F: 10M) with a mean age of 35.2 years (range: 20-54) were enrolled. On Day 1 the mean (+/- SD) maximum plasma concentration (Cmax) of treprostinil was 0.574 +/- 0.22 ng/mL, occurring at a median time of 4 hours (range: 2-6 hrs). In comparison, the Day 8 mean (+/- SD) Cmax was 0.615 +/- 0.32 ng/mL, occurring at a median time of 4 hours (range: 1-6 hrs). [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 Cmax (+/- SD) was 0.810 +/- 0.491 ng/mL, occurring at a median time of 14 hours (range: 6-20 hrs) following the morning dose. [Figure 2]. This indicates that maximum 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 adverse events (AEs) occurred in 7 subjects and primarily included known prostacyclin class-effect related AEs (e.g., headache, diarrhea, and jaw pain).

1.2.3 Remodulin Experience

Remodulin (treprostinil sodium) Injection is a sterile solution of treprostinil sodium formulated for subcutaneous or intravenous administration using an ambulatory infusion pump. The toxicity profile of treprostinil delivered by continuous subcutaneous infusion has been extensively evaluated. The studies conducted include the complete International Conference on Harmonisation (ICH) battery of genetic toxicology studies; acute, single-dose, intravenous and oral toxicity studies in rats and mice; acute, single-dose, subcutaneous toxicity studies in rats and dogs; repeat dose, continuous subcutaneous infusion toxicity studies up to 6 months in duration in rats and dogs; and reproductive toxicity studies in rats (fertility, teratology and pre/postnatal) and rabbits (teratology).

The clinical development of subcutaneous Remodulin included two international, placebo-controlled, pivotal studies (13 countries, 40 centers). These two studies were identical in design and together enrolled 470 patients with PAH. Patients receiving Remodulin had clinically significant improvements in exercise tolerance (both distance walked and associated dyspnea), symptoms of PAH, physician-based dyspnea-fatigue rating, hemodynamic variables, and quality of life (physical domain) compared to patients receiving placebo treatment. Open-label efficacy data collected by the clinical centers indicate that the clinical benefits of Remodulin are maintained with long-term treatment.

The most frequent adverse events (AEs) associated with Remodulin therapy were related to the pharmacological properties of Remodulin and were generally not serious. These prostacyclin-related AEs fell into two categories: those related to the local prostaglandin action at the subcutaneous infusion site (e.g., infusion site pain and reaction), and those related to systemic effects that are characteristic of prostacyclin (e.g., diarrhea, headache, nausea). Localized subcutaneous infusion site pain and reaction were common (85% of Remodulin-treated patients), but were generally manageable, typically resulted in withdrawal of treatment in a low percentage of patients (10-15%), did not limit increases in dose, and tended to improve with time on therapy. Remodulin was not 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. Thus, Remodulin was shown to be a safe and effective treatment option for patients with PAH.

To date, well over 10,000 patients/subjects have been exposed to Remodulin from single administration to patients receiving continuous infusion of Remodulin for greater than 10 years. The Remodulin (treprostinil sodium) Injection approved product label should be reviewed for additional details on the results of studies undertaken during the development of Remodulin.

Although Remodulin is an effective agent given by subcutaneous or intravenous delivery, these forms of administration have patient convenience limitations, including the need for an ambulatory infusion device and pain at the site of infusion associated with subcutaneous delivery. Thus, an orally available formulation of treprostinil would be of tremendous benefit. However, the sodium salt of treprostinil (i.e., Remodulin) is not an appropriate candidate to develop as a solid-dose oral compound. A more desirable salt of treprostinil (diethanolamine) is therefore being investigated.

1.3 Rationale for Development of Study Drug in Disease/Condition

Prostacyclin (PGI_2) is a potent vasodilator and inhibitor of platelet aggregation that is produced by vascular endothelium. A synthetic salt of prostacyclin (i.e.Flolan®) was developed and has demonstrated the clinical utility of prostacyclin in the treatment of pulmonary hypertension and other vascular diseases. Unfortunately, due to its very short half-life and chemical instability, Flolan must be continuously infused by intravenous delivery. Various analogues have been developed that have overcome some of these limitations, but the few orally active agents have remained limited by their short half-life and poor solubility. Remodulin® (treprostinil sodium) is a chemically stable, longer acting analogue that has shown clinical effectiveness when administered by the continuous subcutaneous and intravenous routes. Recent data indicate that a new salt form of treprostinil, diethanolamine, may be delivered by the oral route. It is expected that an oral formulation of treprostinil will not only allow patients suffering from PAH to benefit

from the simplicity of an oral dosage form but may also facilitate the treatment of either previously untreated conditions or improve the treatment of conditions that are not adequately controlled with current therapies.

1.4 Clinical Hypothesis

This open-label study will evaluate the safety of continued therapy with UT-15C SR in subjects who completed assessments in Protocol TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308, or any other study evaluating UT-15C SR in patients with PAH. The study will also provide information about long-term dosing patterns. Finally, a 6-Minute Walk Test with Borg Dyspnea Score to be conducted after subjects have completed one year of treatment with UT-15C SR will provide information about the efficacy of long-term treatment.

With Amendment 5, subjects will have the option of modifying their dosing regimen from BID to TID. The intention of the dosing modification from BID to TID is to deliver a more sustained plasma concentration of treprostinil thereby providing systemic exposure to drug that resembles the approved parenteral product, Remodulin, while reducing the occurrence and/or severity of prostacyclin-related adverse events previously associated with the twice daily regimen.

The transition from BID to TID dosing should be made at the discretion of the investigator taking into account the subjects current disease state and tolerability of UT-15C.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The objectives of this study are to:

- Provide, or continue to provide, UT-15C SR for eligible subjects who participated in protocols TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308 or additional UT-15C SR clinical protocols.
- Assess the long-term safety of UT-15C SR in these subjects through assessment of adverse events and laboratory parameters.
- Assess the effect of continued therapy with UT-15C SR on exercise capacity after one year of treatment.

2.2 Study Endpoints

The safety endpoints are as follows:

- Adverse events
- Clinical laboratory parameters

PAH concomitant medications also will be documented.

Efficacy will be assessed by a 6-Minute Walk Test and Borg Dyspnea Score to be conducted after each subject has completed one year of therapy with UT-15C SR.

3 EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study. Each subject's visit schedule will allow assessments after defined periods of exposure to UT-15C SR (3, 6, 12, 24 and 36 months total exposure). The study will continue with yearly visits beyond 36 months until either UT-15C SR is approved by the appropriate regulatory authorities or the study is discontinued by the sponsor. Therefore, the actual date of each visit will be determined by the date on which the subject first received UT-15C SR (e.g., the date of study drug initiation in TDE-PH-301, TDE-PH-302, or TDE-PH-308 for subjects who were randomized to active therapy in those trials, and the date of UT-15C SR initiation in this study for subjects who were randomized to placebo in the previous controlled trial). Note that the TDE-PH-202, TDE-PH-203, TDE-PH-205 studies are open-label design and therefore will follow the regimen for subjects receiving UT-15C SR.

Subjects enrolled from the TDE-PH-202 study who were in Dose Groups 1 or 2 and permanently discontinued treatment may enter the study if they undergo all premature termination assessments prior to discontinuing study drug and complete all remaining scheduled study visits and assessments (with the exception of the hemodynamic measurements) through Week 12. These subjects should follow the same procedures as subjects who received placebo in the previous study and will begin on a dose of 0.25mg BID.

Subjects randomized to UT-15C SR in Protocol TDE-PH-301, TDE-PH-302, or TDE-PH-308 will complete visits 2-5 and yearly visits thereafter, while subjects randomized to placebo in Protocol TDE-PH-301, TDE-PH-302, or TDE-PH-308 will complete visits 1-5 and yearly visits thereafter. A 6-Minute Walk test and Borg Dyspnea Score will be conducted at the visit occurring 12 months after the subject's initial exposure to UT-15C SR.

3.2 Overall Schedule of Times and Events

The overall schedule of Time and Events is shown in Table 3.2. Note that the timing of each visit depends upon when the subject first received UT-15C SR (e.g. whether the subject was assigned to active or placebo treatment in Protocol TDE-PH-301, TDE-PH-302, or TDE-PH-308). Subjects receiving placebo in the previous study, or subjects enrolled from the TDE-PH-202 study who are beginning a dose of 0.25mg BID, must be contacted weekly by telephone (at a minimum) during the first 12 weeks of the open-label study to ensure subject safety. More specifically, these calls should assess study drug dose titration needs, potential adverse events, concomitant medication usage and PAH signs and symptoms. Monthly telephone calls (at a minimum) must be conducted for all subjects actively participating in TDE-PH-304, regardless of study drug allocation (UT-15C SR or placebo) in the previous study, to assess dose titration needs, potential adverse events, concomitant medication usage and PAH signs and symptoms. In addition to the scheduled study visits, all subjects must be seen in the clinic no less than once every six months for routine standard of care medical evaluation.

Subjects enrolling from the TDE-PH-203 and TDE-PH-205 studies will transition on the same dose they were receiving at the end of the study. Study visits for the TDE-PH-304 protocol will be based on the date the subject first received active UT-15C in their respective preceding study.

Table 3.2. Time and Events

	Visit [4,5,6,7]						
Assessment	**Visit 0-1 (Weeks 1-12) [3]**	**1**	**2**	**3**	**4**	**5+[8]**	**EXIT[9]**
Adverse Events	X	X	X	X	X	X	X
PAH Concomitant Medications	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
6-Minute Walk Test/Borg Dyspnea Score [1]				X			
Clinical Laboratory Parameters [2]		X	X	X	X	X	X
Drug Accountability/Compliance	X	X	X	X	X	X	X

[1] **6-Minute Walk Test/Borg Dyspnea Score** as described in Appendix A. conducted 3 to 6 hours after the morning dose of UT-15C SR.
[2] **Laboratories** to be collected are described in Appendix B.
[3] **Weekly telephone calls** (at a minimum) required during Weeks 1-12 for subjects randomized to placebo in TDE-PH-301, 302, or 308 to assess dose titration needs, potential adverse events, concomitant medication usage and PAH signs and symptoms. Also applies to subjects enrolled from the TDE-PH-202 study who are beginning a dose of 0.25mg BID.
[4] **Visit windows** are ± 1 month from the scheduled number of months from first exposure to UT-15C SR, except for Visit 1, which is ± 2 weeks.
[5] **VISIT 1** – Only for subjects randomized to placebo in TDE-PH-301, 302, or 308; 3 months after subject's first exposure to UT-15C. Also applies to subjects enrolled from the TDE-PH-202 study who are beginning a dose of 0.25mg BID.
VISIT 2 – 6 months after subject's first exposure to UT-15C SR.
VISIT 3 – 12 months after subject's first exposure to UT-15C SR.
VISIT 4 – 24 months after subject's first exposure to UT-15C SR.
VISIT 5 – 36 months after subject's first exposure to UT-15C SR.
[6] **Weekly telephone call** required for 4 weeks for all subjects who transition from a BID to TID regimen to assess dose titration needs, potential adverse events, concomitant medication usage and PAH signs and symptoms.
[7] **Monthly telephone calls** (at a minimum) required for all subjects participating in TDE-PH-304 to assess dose titration needs, potential adverse events, concomitant medication usage and PAH signs and symptoms.
[8] **Visits beyond Visit 5** will occur yearly until either the drug receives regulatory approval in a particular region or the sponsor discontinues the study. Assessments after visit 5 will include adverse events, PAH concomitant medications, concomitant medications, clinical laboratories, and compliance/drug accountability.
[9] **EXIT** – If the subject discontinues from the study between scheduled visits, every effort should be made to obtain the exit assessments just prior to termination from the study.

3.3 Clinical Assessments

3.3.1 Efficacy

A 6-Minute Walk Test with Borg Dyspnea Score (described in Appendix A) will be conducted at Visit 3, 12 months from the subject's first exposure to UT-15C SR. The 6-Minute Walk Test should be conducted approximately 3 to 6 hours after the morning dose of UT-15C SR.

3.3.2 Safety

3.3.2.1 Clinical Laboratory Assessments

Clinical laboratory parameters will be assessed at each study visit. Laboratories to be assessed at the study visits are listed in Appendix B.

3.3.2.2 Adverse Event Assessment

Adverse event reporting instructions for protocols TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, and TDE-PH-308 will be followed in the open-label study. Adverse events will be reported continuously, as in protocols TDE-PH-202, TDE-PH-301, TDE-PH-302, and TDE-PH-308 and documented on the Case Report Form (CRF). Any AEs that were ongoing at the time of discharge from protocols TDE-PH-202, TDE-PH-203, TDE-PH-205,TDE-PH-301, TDE-PH-302, or TDE-PH-308 should be recorded as a part of the medical history in the open-label study. Section 9 and Appendix C provide the guidelines and definitions for recording of AEs.

For subjects transitioning from a BID to TID regimen, additional adverse event information will be collected via weekly phone contact for at least four weeks from the date of transition.

3.3.2.3. Concomitant Medications

In this open-label study, there are no restrictions on concomitant medications, with the exception of the addition of prostanoid therapy. If chronic parenteral prostanoid therapy is added for the treatment of worsening PAH, the subject will be discontinued from the study. Short term, parenteral prostanoid therapy may be initiated if required (e.g., the patient is temporarily unable to take oral medications). If prostanoid therapy is initiated for any other reason than worsening PAH, eligibility for continued participation in this study will need to be reviewed by the Medical Monitor on a case by case basis. For subjects enrolling into TDE-PH-304 from the TDE-PH-203 study continued chronic use of inhaled treprostinil (Tyvaso®) is acceptable.

ERAs and PDE-5 inhibitors may be added or withdrawn at any time. Concomitant PDE-5 inhibitors, ERAs, and other medications related to the subject's treatment will be collected at each study visit and recorded in the CRF.

3.4 Number of Centers

The study will be an international, multi-center study with approximately 118 centers participating. All centers participating in protocols TDE-PH-202, TDE-PH-301, TDE-PH-302, and/or TDE-PH-308 or other UT-15C SR clinical protocols will participate in this open-label study.

3.5 Number of Subjects

Approximately 900 subjects will be enrolled across all sites participating in either TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308. Additional subjects may be enrolled from other clinical protocols evaluating UT-15C SR in subjects with PAH. All subjects successfully completing all assessments in either protocol TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308 or other UT-15C SR clinical protocols are eligible for participation.

Subjects randomized into Dose Group 1 or Dose Group 2 in the TDE-PH-202 study who permanently discontinue study drug during the 12-week Treatment Phase due to clinical worsening are eligible for entry into the TDE-PH-304 if they undergo all premature termination assessments prior to discontinuing study drug and complete all remaining scheduled study visits and assessments (with the exception of the hemodynamic measurements) through Week 12. Such subjects should start treatment with UT-15C in the open-label study at 0.25 mg BID.

3.6 Estimated Study Duration

The estimated study duration for each subject is at least 36 months from the point of transition from protocol TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308 to the end of the open-label study. The study will continue until either UT-15C SR receives regulatory approval in a region or the study is discontinued by the sponsor.

4 SUBJECT ELIGIBILITY

4.1 Subject Inclusion Criteria

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

1. The subject has remained on study drug and completed all assessments during the Treatment Phase of the previous study (TDE-PH-202, TDE-PH-203, TDE-PH-205,TDE-PH-301, TDE-PH-302, or TDE-PH-308 (or other studies evaluating PAH))

OR

The subject permanently discontinued study drug during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308) due to clinical worsening, completed premature termination assessments prior to discontinuing study drug, completed all remaining scheduled study visits AND received placebo during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308).

OR

The subject was randomized into Dose Group 1 or Dose Group 2 in the TDE-PH-202, permanently discontinued study drug during the 12-week Treatment Phase due to clinical worsening, completed all premature termination assessments prior to discontinuing study drug and completed all remaining scheduled study visits and assessments (with the exception of the hemodynamic measurements) through Week 12. Such subjects should start treatment with UT-15C in the open-label study at 0.25 mg BID.

2. The subject voluntarily gives informed consent to participate in the study.

3. Women of child bearing potential include 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]. Sexually active women of childbearing potential must use two effective forms of contraception during the length of the study. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device (IUD), (4) partner vasectomy, or (5) abstinence. Males participating in the study must use a condom during the length of the study, and for at least 48 hours after discontinuing study medication.

4.2 Subject Exclusion Criteria

1. The subject permanently discontinued study drug during the previous study (TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308) due to treatment related adverse events.

2. The subject permanently discontinued study drug during the Treatment Phase of the previous study (TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, or TDE-PH-308) due to clinical worsening (as defined in those study protocols) and did not undergo premature termination assessments prior to discontinuing study drug, and/or did not complete all remaining study visits through the final scheduled visit.

3. The subject permanently discontinued study drug during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308) due to clinical worsening, completed premature termination assessments prior to discontinuing study drug, completed all remaining scheduled study visits AND received UT-15C SR during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308).

   Subjects enrolled in the TDE-PH-202 study who were randomized into the iMTD group who clinically worsen may not participate. Subjects who permanently discontinue study drug during

the 12-week Treatment Phase due to treatment related adverse events are not eligible even if they complete all remaining scheduled study visits. Subjects who permanently discontinue study drug during the 12-week Treatment Phase and do not undergo premature termination assessments prior to discontinuing study drug and/or who do not complete all remaining study visits through the Week 12 visit are also not eligible.

4. The subject must not have developed any concurrent illness or condition during the conduct of the previous study, including but not restricted to, sleep apnea, chronic renal insufficiency, anemia, uncontrolled systemic hypertension or left sided heart disease, unless their physician feels that entry into this study would not be detrimental to their overall health.

5 SUBJECT ENROLLMENT

5.1 Treatment Assignment

All subjects will receive UT-15C SR during the open-label study.

5.2 Randomization

This study is not randomized.

5.3 Blinding

This study is not blinded.

6 DRUGS AND DOSING

6.1 Drug Dosage, Administration and Schedule

UT-15C SR tablets will be provided as 0.25, 0.5, 1, and 2.5 mg tablet strengths. They may also be provided as 0.125 mg strength, if available. The 0.125, 0.25, 0.5, 1, and 2.5 mg tablets are colored blue, green, white, yellow, and pink, respectively.

For subjects who were randomized to placebo in protocols TDE-PH-301, TDE-PH-302, or TDE-PH-308, dosing of UT-15C SR will be initiated and optimized as in the previous protocol, including all safety monitoring including periodic telephone contacts. That is, the first dose of UT-15C SR (0.25 mg) should be taken by the subject immediately following (~ 10 minutes) a meal while at the study site. The subject should remain close to the study site for approximately 3 to 6 hours for periodic observation and monitoring of possible AEs.

Subjects who were randomized to UT-15C SR, or were receiving active therapy in the previous trial will begin open-label therapy at the same dose and regimen (e.g. BID or TID) they were receiving at the final visit in the previous trial, and subsequent dose adjustments will be made based on symptoms of PAH and AEs.

With Amendment 5, subjects may now receive UT-15C either twice (BID) or three (TID) time daily. The decision to transition subjects from BID to TID is up to the discretion of the principal investigator, and not a requirement of the protocol.

The dose of UT-15C SR at the time the subject is discharged from each study visit should be recorded on the CRF.

6.1.1 Twice Daily Dosing Regimen

The next dose of study drug should be taken the following morning. At this time oral dosing of UT-15C SR will be initiated at 0.25 mg twice daily (every 12 hours +/- 1 hour) immediately following (~10 minutes) breakfast and dinner. Subjects must be instructed to take the appropriate amount of 0.25, 0.5, 1, and/or 2.5 mg tablets based upon their given dose. In general, the dose of study drug should be increased in 0.25 to 0.5 mg increments every 3 days, in the absence of dose-limiting drug-related side effects, to ensure the subject receives the optimum clinical dose throughout the study. The 0.125 mg strength, if available, may be used throughout the study if a 0.25 mg dose increase is not tolerated and an intermediate dose is required. Dose changes should be conducted under appropriate medical supervision in consultation with the study site.

6.1.2 Transition from Twice to Three Times daily Dosing

For subjects enrolled in the TDE-PH-304 study who are receiving UT-15C twice daily, dosing frequency may be transitioned from BID to TID. For applicable subjects, it is recommended to reduce the total daily dose administered during BID dosing by approximately 25% and divide the total daily dose into a TID regimen using the appropriate tablet strength(s). Please see Table 6-1 below for examples of transitioning from BID dosing to TID dosing. However, dose modification should occur in accordance with investigator judgment.

Table 6-1 Example Transition from Twice Daily to Three Times Daily Dosing of UT-15C

BID Dosing Regimen	**Total Daily Dose with BID Dosing**	**Total Daily Dose with BID Dosing Reduced by 25%**	**TID Dosing Regimen**	**Total Daily Dose with TID Dosing**
3 mg BID	6 mg	4.5 mg	1.5 mg TID	4.5 mg
5 mg qAM; 5.25 mg qPM	10.25 mg	7.6875 mg	2.5 mg TID	7.5 mg
6 mg BID	12 mg	9 mg	3 mg TID	9 mg
6.5 mg qAM; 6.625 mg qPM	13.125 mg	9.844 mg	3.25 mg TID	9.75 mg
10 mg BID	20 mg	15 mg	5 mg TID	15 mg
11 mg qAM; 11.5 mg qPM	22.5 mg	16.875 mg	5.5 mg TID	16.5 mg
13 mg BID	26 mg	19.5 mg	6.5 mg TID	19.5 mg
17.125 mg qAM; 17.25 mg qPM	34.375 mg	25.781 mg	8.5 mg TID	25.5 mg

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. If dose titration is considered appropriate, site personnel will instruct the subject to modify their dose; dose changes will be recorded in source documentation and CRF by site personnel.

6.1.3 Three Times (TID) Daily Dosing Regimen

For subjects entering the TDE-PH-304 study receiving a TID dosing regimen (e.g. TDE-PH-205), or for those subjects transitioning from BID to TID dosing, the dosing regimen should be managed as follows:

- TID (every 6-8 hours) with food
- Increases should occur in increments of 0.125 or 0.25 mg TID every 3 days.

In general, the dose of study drug should be increased in 0.125 to 0.25 mg increments every 3 days, in the absence of dose-limiting drug-related side effects, to ensure the subject receives the optimum clinical dose throughout the study. The 0.125 mg strength, if available, may be used throughout the study if a

0.25 mg dose increase is not tolerated and an intermediate dose is required. Dose changes should be conducted under appropriate medical supervision in consultation with the study site.

6.1.4 Dosing of Study Medication in Relation to Meals

Subjects should take study drug approximately every 12 hours (+/- 1 hour) for BID dosing and every 6 – 8 hours for TID dosing, with approximately 240 mL (8 ounces) of water or other beverage (e.g. juice, milk, soda, etc.) immediately after (~ 10 minutes) consuming food (approximately 250 calories).

Subjects should be instructed to be careful not to break, chew, or disrupt the integrity of the tablet as this will result in inappropriate delivery of the active ingredient. If the tablet is inadvertently damaged during administration, the subject should contact site personnel in order to be monitored for the onset of symptoms due to possible overdose.

6.2 Compliance

At each visit, the Investigator or designee will evaluate the amount of UT-15C SR provided to each subject and any returned medication (as required for drug accountability purposes), and compare this accounting with the subject's dosing pattern to obtain an estimate of overall compliance. Each subject will also be asked at each visit whether he or she is in compliance with dosing instructions. If it is determined that a subject is not compliant with study drug then site personnel should re-educate the subject on proper dosing compliance. Continued non-compliance may lead to discontinuation of the subject, after consultation between the Investigator and sponsor.

7 EXPERIMENTAL PROCEDURES

7.1 Open-Label Phase

All values collected at the subject's respective final visit in protocol TDE-PH-202 TDE-PH-203, TDE-PH-205, TDE-PH-301 or TDE-PH-308 and TDE-PH-302 will serve as the baseline assessments for the open-label study.

Subjects receiving placebo in the previous study must be contacted weekly by telephone (at a minimum) during the first 12 weeks of the open-label study and, if necessary, brought in for clinic visits in the first several months of the study to ensure subject safety. This also applies to subjects enrolled from the TDE-PH-202 study (Dose Groups 1 or 2) who are beginning a dose of 0.25mg BID.

Monthly telephone calls (at a minimum) must be conducted for all subjects actively participating in the open-label study, regardless of study drug allocation (UT-15C SR or placebo) in the previous study.

In addition to the scheduled study visits, as listed below, all subjects must be seen in the clinic no less than once every six months for routine standard of care medical evaluation.

Weekly telephone calls (required Weeks 1-12; only for subjects randomized to placebo in previous study). This also applies to subjects enrolled from the TDE-PH-202 study (Dose Groups 1 or 2) who are beginning a dose of 0.25mg BID.

- Adverse events
- PAH concomitant medications
- Concomitant medications

Drug accountability / compliance

Weekly telephone calls (required for 4 weeks for subjects who transition from BID to TID dosing)

- Adverse Events
- PAH concomitant medications
- Concomitant medications
- Drug accountability/compliance

Monthly telephone calls (required for all subjects participating in open-label study)
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Drug accountability / compliance

Visit 1 (three months after first dose of UT-15C SR; only for subjects randomized to placebo in previous study). This also applies to subjects enrolled from the TDE-PH-202 study (Dose Groups 1 or 2) who are beginning a dose of 0.25mg BID.
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

Visit 2 (six months after first dose of UT-15C SR)
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

Visit 3 (12 months after first dose of UT-15C SR)
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance
- 6-Minute walk test/borg dyspnea score

Visit 4 (24 months after first dose of UT-15C SR)
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

Visit 5 (36 months after first dose of UT-15C SR)
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

Yearly visits beyond 36 months
- Adverse events
- PAH concomitant medications
- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

Exit (premature discontinuation)
- Adverse events
- PAH concomitant medications

- Concomitant medications
- Clinical laboratories
- Drug accountability/compliance

8 STUDY TERMINATION

8.1 Subject Discontinuation

A subject may voluntarily withdraw or be withdrawn from the study 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

If a subject is discontinued prematurely, the Investigator must provide an explanation in the CRF (Investigator's Comment Log) and complete the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues prematurely due to an AE, the subject will be followed until the Investigator determines the AE has resolved, the AE is no longer considered clinically significant, the subject is lost to follow-up, or for 30 days following discontinuation of UT-15C.

8.2 Study Discontinuation

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 adverse events or adverse events that are unacceptable in nature, severity, or frequency. The sponsor reserves the right to discontinue the study for any reason at any time. In the event the sponsor discontinues the study, an EXIT visit for each subject should be scheduled.

8.3 Site Discontinuation

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
- U.S. FDA, European, or national regulations are not observed
- The protocol is violated
- Changes in personnel or facilities adversely affect performance of the study

9 ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical experience occurring to a subject during a clinical trial whether or not it is related to the study drug. An AE may include an intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. AEs may also include worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

9.1.2 Serious Adverse Event

A serious adverse event (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
  - Planned hospitalizations (e.g., admission for elective surgery or right heart catheterization) do not qualify as SAE's
- 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 Expected Adverse Event

Adverse events associated with progression of PAH:

An expected event that is related to the progression of a subject's PAH is defined in Appendix D, Part A. All events that occur during the course of the study that are included on this list and felt to be related to progression of disease by the Investigator should NOT be recorded as AEs in the CRF as the most relevant PAH symptoms will be evaluated and recorded as an efficacy endpoint and all other events will be captured as disease related events. If the event is either serious or unusual with respect to intensity, frequency, or duration, OR there is a reasonable possibility that it may have been caused by study drug, it must be recorded as an AE in the CRF.

Adverse events known to be associated with treprostinil therapy:

An expected AE for UT-15C is defined as any AE that is defined in terms of nature, severity, or frequency in the current Investigators' Brochure and in Appendix D, Part B. When an adverse event may be attributed to the progression of pulmonary hypertension or UT-15C SR (e.g., listed in both Parts A and B) it must be recorded as an AE in the CRF if the event is either serious or unusual with respect to intensity, frequency, or duration, OR there is a reasonable possibility that it may have been caused by study drug.

Expected events attributable to UT-15C (e.g., listed in Part B only) must always be recorded as AEs in the CRF.

If an event listed in Appendix D Part A or B occurs during the conduct of the trial, it will not give rise to submission of an expedited safety report despite being considered serious and possibly attributable to the study drug, unless the United Therapeutics Medical Monitor, responsible for assessing the case considers it to be unusual (e.g., more severe than expected) and therefore reportable. The data regarding such events will always be recorded in the clinical study database, regardless of reportability.

9.2 Documentation of Adverse Events

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate CRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome will also be documented in the CRF (see Appendix C 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 CRF page, not the individual signs and symptoms.

All adverse events 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 30 days following discontinuation of UT-15C. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. CRF 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 by fax or email [redacted] within 24 hours of awareness. A completed SAE report form along with any relevant hospital records and autopsy reports should be faxed to the Drug Safety Department at United Therapeutics Corporation. A follow-up SAE report form should be forwarded to the Drug Safety Department at United Therapeutics Corporation within 48 hours of the receipt of any new/updated information. The Investigator must also promptly notify the Investigational Review Board (IRB) or Ethics Committee (EC) of the SAE, including any follow-up information according to the guidelines set forth by the IRB or EC.

9.4 Safety Reports

In accordance with FDA, European, and national regulations, the Sponsor will notify the FDA, other competent authorities, and all participating investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC. If an event listed in Appendix D Part A or B occurs during the conduct of the trial, it will not give rise to submission of an expedited safety report despite being considered serious and possibly attributable to the study drug, unless the United Therapeutics Medical Monitor, responsible for assessing the case considers it to be unusual (e.g., more severe than expected) and therefore reportable. The data regarding such events will always be recorded in the clinical study database, regardless of reportability.

9.5 Pregnancy

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Report Form and either faxing or emailing this form to [redacted] Subjects who

become pregnant during the trial will be withdrawn from active participation in the trial and will discontinue study drug after an appropriate period of down-titration.

United Therapeutics Global Drug Safety will follow up with the Investigator each trimester to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy 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.

10 DATA MANGEMENT AND STATISTICS

Completed CRFs will be forwarded to United Therapeutics or its designee for processing. A quality-assured computerized database will be constructed. Data will be listed and also will be summarized either in tabular and/or graphical presentations.

The safety of UT-15C SR will be assessed using laboratory assessments and reports of adverse events. All reported adverse events will be assigned MedDRA terms which will be listed and summarized according to intensity, seriousness and causality.

Efficacy assessments (6-Minute Walk/Borg Dyspnea Score) may be compared to assessments in Protocols TDE-PH-202, TDE-PH-203, TDE-PH-205, TDE-PH-301, TDE-PH-302, TDE-PH-308, or TDE-PH-304, as appropriate. Doses of UT-15C SR will be listed, summarized and analyzed for trends over time.

11 PACKAGING AND FORMULATION

11.1 Study Drug Content

United Therapeutics will supply UT-15C SR for administration in the study. UT-15C SR tablets will be provided as 0.25, 0.5, 1, and 2.5 mg strengths and may also be provided as a 0.125 mg strength, if available. UT-15C SR 0.125 mg (blue), 0.25 mg (green), 0.5 mg (white), 1 mg (yellow), and 2.5 mg (pink) tablets will be provided in child resistant bottles each containing 100 tablets, or in other appropriate packaging configurations as may be required as more experience with long-term dosing requirements is obtained.

11.2 Study Drug Labeling

Each bottle and/or other packaging (e.g., kits/cartons) for UT-15C SR will be labeled with at least the following information: study drug, strength, quantity, manufacture date, lot number, sponsor name and address, and storage conditions.

11.3 Study Drug Storage and Handling

All study drug will be stored in accordance with label specified storage conditions. UT-15C SR should not be frozen or exposed to heat.

Subjects should be instructed to return all study drug, including empty bottles or other containers, to the appropriate study personnel for drug accountability and compliance assessments, as appropriate.

11.4 Study Drug Supply and Return

Study sites will be supplied with a sufficient quantity of UT-15C SR to begin enrollment in the study. Appropriate arrangements will be made for resupply with respect to each subject's visit schedule. All unused study drug dispensed to the subject should be returned to the study site (including empty and unopened bottles).

11.5 Study Drug Accountability

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records 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.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 Regulatory Requirements

The study will be conducted in accordance with ICH and 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 safety 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 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 informed consent form prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject and the original will be retained in the study site's records.

12.3 Institutional Review Board/Independent Ethics Committee Approval

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 informed consent form 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 informed consent form, the Investigator is responsible for obtaining IRB/EC approval of these amended documents prior to implementation. Copies of the IRB/EC correspondence and approval letters must be sent to the Sponsor.

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

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

12.4 Prestudy Documentation Requirements

Before the commencement of the clinical trial, the following documents will be provided to the site: Investigator's Brochure, Protocol, Informed Consent Form, Budget Agreement, and Case Report Form.

The site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, IRB/EC Composition and

Roster, IRB/EC approval letters for protocol and informed consent, and Curriculum Vitae of study staff listed on the 1572.

12.5 Subject Confidentiality

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, the FDA or other 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 the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects and any report published will not identify the subject's name.

12.6 Reporting of Clinical Trial Results

The timely communication of scientifically valid results, positive and negative, from this clinical trial will occur. Avenues for such public communications may include the following: peer-reviewed publications of original research and scientific, nonpromotional summaries on a publicly accessible registry (i.e., a Web site). A committee of principal investigators participating in the clinical trial and enrolling the highest number of subjects will oversee the publication of study results.

The guidelines such as the Good Publication Practice (GPP) guidelines for pharmaceutical companies (gpp-guidelines.org), and guidelines sponsored by the International Committee of Medical Journal Editors and the Pharmaceutical Manufacturers Association (PhRMA) will be endorsed. In addition, an attempt will be made to fulfill any country specific regulatory requirements for publication of clinical trials conducted within that country.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

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

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/Ethics Committee 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, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. For investigators in the European Economic Area (EEA), the study records should be maintained for at least 15 years after study discontinuation. The Investigator must notify United Therapeutics Corporation before any disposal or change in location of study records.

13.3 Study Monitoring and Data Collection

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

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

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