A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF)

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CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	28 December 2016
Amendment 1	15 September 2017
Amendment 2	01 February 2018
Amendment 3	20 February 2019
Amendment 4	12 August 2019

LIST OF CONTACTS FOR STUDY

Contract Research Organization	
Study Sponsor	
Central Clinical Laboratories	

INVESTIGATOR'S AGREEMENT

I have read the attached Protocol Amendment 4 entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF)" dated 12 August 2019 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 any local regulations per country.

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

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

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

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF)
Study Phase	3
Indication	Pulmonary hypertension (PH) associated with left-sided heart failure and preserved ejection fraction
Primary Objective	The primary objective of this study is to assess the effect of oral treprostinil compared with placebo on change in exercise capacity as measured by change in 6-Minute Walk Distance (6MWD) from Baseline to Week 24 in subjects with PH associated with HFpEF.
Secondary Objectives	To assess the effect of oral treprostinil compared with placebo on the following: • Change in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels from Baseline to Week 24 • Time to the first clinical worsening event where clinical worsening is defined by at least 1 of the following: o Hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or heart failure) o Outpatient administration of intravenous (IV) diuretics o Decrease in 6MWD >15% from Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study) at 2 consecutive visits on different days (except at Week 24) o Death (all causes) • Change in World Health Organization (WHO) Functional Class from Baseline to Week 24
Exploratory Objectives	To assess the effect of oral treprostinil compared with placebo on the following: • Change in 6MWD from Baseline to Weeks 6, 12, and 18 • Change in Borg dyspnea score from Baseline to Weeks 6, 12, 18, and 24

	• Change in WHO Functional Class from Baseline to Weeks 6, 12, and 18 • Change in NT-proBNP levels from Baseline to Week 12 • Change in glycated hemoglobin (HbA1c) from Baseline to Week 24 • Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from Baseline to Week 24 • Optional evaluation of biomarkers (specific targets to be determined) from Baseline to Week 24 • Optional evaluation of pharmacogenomics
Study Design	A multicenter, randomized, double-blind, placebo-controlled, 24-week, parallel-group study
Sample Size	Approximately 310 subjects will be enrolled and randomly allocated (1:1) to receive oral treprostinil or placebo, stratified by Baseline 6MWD. Using an allocation ratio of 1:1 between oral treprostinil and placebo, a sample size of 263 subjects would provide 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30-meter between-treatment difference in the change from Baseline to Week 24 in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 310 subjects to account for a discontinuation rate of approximately 15%.
Summary of Subject Eligibility Criteria	Eligible subjects must be between 18 and 85 years of age at the time of signing informed consent, have a primary diagnosis of WHO Group 2 PH, and have the following documented by right heart catheterization (RHC): a pulmonary artery pressure mean (PAPm) of ≥25 mmHg, a pulmonary capillary wedge pressure (PCWP) of >15 mmHg but ≤30 mmHg, and a pulmonary vascular resistance (PVR) of ≥3.0 Wood units (≥240 dynes*s/cm^5). Subjects can also qualify if they have a positive fluid challenge during the RHC that is used to determine eligibility. In cases where a PCWP is not available or deemed unreliable, a left ventricular end-diastolic pressure may be used to determine eligibility. In addition, subjects must have a left ventricular ejection fraction by echocardiogram (ECHO) obtained during Screening (prior to randomization) of at least 45%. Subjects must have pulmonary function tests conducted within 6 months of Screening or during the Screening phase to confirm that total lung capacity is at least 60% of the predicted value, forced expiratory volume at 1 second is at least 50% of the predicted value, and diffusing capacity of

	the lungs for carbon monoxide (DLCO) is at least 40% of the predicted value (unadjusted, or adjusted for alveolar volume). The Baseline 6MWD must be at least 150 meters and subjects must not have received PAH therapies within 30 days of randomization. The only exception to this is that subjects can be taking chronic doses of an approved phosphodiesterase type 5 inhibitor (PDE5-I) as long as they have been on a stable dose for at least 90 days prior to randomization and have had an RHC that establishes eligibility at least 30 days after being on a stable dose of their PDE5-I inhibitor. If the Investigator does not intend to keep a subject on their PDE5-I therapy, it must be stopped at least 30 days prior to randomization. Subjects on a chronic medication for heart failure must be on a stable dose for ≥30 days prior to randomization. The exception is with changes of anticoagulants and/or diuretics; these medications should not be newly started or stopped within 30 days of randomization and no healthcare provider prescribed dose change should occur within 7 days of randomization. Eligible subjects will have a body mass index of ≤45 kg/m^2.
Drug Dosage and Formulation	Subjects will receive oral treprostinil sustained-release tablets or matching placebo. Study drug will be provided in 0.125-, 0.25-, 1-, and 2.5-mg sustained-release tablets to be administered 3 times daily (TID). Following randomization, the first dose of study drug (0.125 mg) should be taken by the subject within 10 minutes of consuming food at the Baseline Visit at the study site. Oral dosing of study drug will then continue at 0.125 mg TID (every 6 to 8 hours) with food. Dose escalation should occur no more frequently than every 72 hours (9 consecutive doses) using only 0.125-mg increments as tolerated. The initial maximum dose allowed will be 2 mg TID. The maximum dose may be increased to 4 mg and then to 6 mg TID, if approved by the independent Data Monitoring Committee (DMC). The DMC will meet after approximately 10, 30, 60, 100, and 200 subjects have been enrolled in the study, or on an ad hoc basis per request of the independent DMC, as necessary. Enrollment will not be stopped during the DMC reviews; however, subjects may not progress to the next highest maximum dose level until the DMC provides their review of the data. Any decision impacting the maximum dose will be relayed to study sites following the DMC meeting. Note that sudden dose escalations or reductions may lead to intolerable

	adverse events (AEs) or worsening of PH, and gradual dose escalations or reductions are recommended to reduce risk to subjects. Placebo will be identical in size, shape, and color to the respective oral treprostinil tablets.
Control Group	Placebo
Route of Administration	Oral
Procedures	*Study Visit Schedule*: Subjects will be assessed during Screening (up to 30 days) and Baseline to determine eligibility for the study. Once randomized, subjects will be dispensed study drug and will take the initial dose of study drug at the study site on the day of randomization. The subject will return to the study site for visits scheduled at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable). Subjects that complete the 24-week treatment period and remain on study drug for the duration will be permitted to enter the open-label extension study. If a subject permanently discontinues study drug prior to Week 24, that subject will be asked to complete a Study Drug Termination Visit and remain in the study through Week 24 and complete study assessments off treatment, but will not be permitted to enter the open-label extension study. The following efficacy and safety assessments will occur during the course of the study: *Efficacy Assessments*: exercise capacity (6MWD and Borg dyspnea score) measured within 3 to 6 hours following the most recent dose of study drug, clinical worsening, WHO Functional Class of PH, NT-proBNP, and KCCQ. *Safety Assessments*: medical history, physical examination, assessment of heart failure signs and symptoms with vital signs, AEs, clinical laboratory parameters, ECHOs, pregnancy testing, and electrocardiograms (ECGs).
Statistical Considerations	The primary hypothesis is that oral treprostinil will increase the distance traversed in the 6-Minute Walk Test (6MWT) at Week 24 over placebo in subjects with PH associated with HFpEF. The effect of oral treprostinil versus placebo on change from Baseline to Week 24 in 6MWD will be analyzed using an analysis of covariance (ANCOVA) with Baseline 6MWD as the covariate.

	The effect of treatment will be formally tested on the following secondary efficacy endpoints: • Time to the first clinical worsening event • Change in NT-proBNP levels from Baseline to Week 24 • Change in WHO Functional Class from Baseline to Week 24 In order to control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed-sequence) testing procedure. Exploratory endpoints will be summarized and analyzed to assess the treatment effect without adjustment for multiplicity.
Sponsor	United Therapeutics Corp. 55 TW Alexander Drive P.O. Box 14186 Research Triangle Park, NC 27709 United States of America

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ACE	Angiotensin-converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin-receptor blockers
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
C_{max}	Maximal drug concentration
CYP	Cytochrome P450
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram(s)
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume at 1 second
GCP	Good Clinical Practices
GDS	Global Drug Safety
GLP	Good Laboratory Practices
HbA1c	Glycated hemoglobin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS/IWRS	Interactive voice or web response system

Abbreviation	Definition
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAPm	Pulmonary artery pressure mean
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary capillary wedge pressure
PDE5-I	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RV	Right ventricle
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SR	Sustained release
TID	3 times daily
US	United States
UT-15C	Treprostinil diolamine or treprostinil diethanolamine; oral treprostinil
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary hypertension (PH) is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance. The World Health Organization (WHO) classifies PH due to left heart disease as WHO Group 2 PH. This classification includes PH due to left ventricular systolic and diastolic dysfunction, valvular heart disease, inflow/outflow tract obstruction, and congenital cardiomyopathies (Simonneau 2013). WHO Group 2 PH accounts for 65% to 80% of all PH cases, making it the most common form of PH (Rosenkranz 2016).

Heart failure with preserved ejection fraction (HFpEF) refers to heart failure with left ventricular diastolic dysfunction in the presence of normal systolic function. Diastolic dysfunction occurs due to increased left ventricular (LV) stiffness and impaired relaxation, resulting in inadequate LV filling. In order to achieve adequate filling during diastole, the pressure within the left atrium increases. PH can result from increased pressures in the pulmonary circulation as a direct consequence of increased left atrium pressure, often referred to as 'postcapillary' PH due to left heart disease. Chronic elevations in left-sided pressures can also trigger endothelial dysfunction and subsequent vascular remodeling, similar to WHO Group 1 pulmonary arterial hypertension (PAH), which is termed 'precapillary' PH (Hussain 2016). Increased levels of endothelin and decreased levels of nitric oxide have been found in subjects with LV dysfunction, and both can contribute to vascular remodeling by causing smooth muscle cell proliferation and hypertrophy (Moraes 2000). HFpEF subjects often have some elements of pre- and postcapillary PH (Hussain 2016).

Heart failure affects 1% to 2% of the adult population in developed countries, and HFpEF represents up to 73% of those cases (Ponikowski 2016). The incidence of PH has recently been reported in up to 80% of HFpEF subjects and is associated with increased morbidity and mortality (Guazzi 2015a).

There are no approved treatments for PH in subjects with left heart disease; however, the efficacy of therapies in WHO Group 1 PAH, along with lack of evidence-based therapies available for the treatment of HFpEF, have stimulated further investigation in this indication (Guazzi 2015b, Hussain 2016, Rosenkranz 2016).

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 prostacyclin.

The pharmacology of treprostinil has been extensively characterized in well-established models, all confirming the suitability of the drug to treat PAH following the subcutaneous (SC), intravenous (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 sustained release [SR]), hereinafter referred to as oral treprostinil, 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 an 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.

Additional nonclinical studies have shown that the observed pharmacological profile of oral treprostinil 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

Oral treprostinil is a novel salt form of Remodulin® (treprostinil) Injection and Tyvaso® (treprostinil) Inhalation Solution, which are approved in the United States (US) to treat subjects with PAH. In addition to the nonclinical studies conducted with oral treprostinil, 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 rats and dogs in toxicity studies for up to 6 months, which supported the chronic administration of Remodulin to subjects.

In addition to the extensive toxicology data with treprostinil sodium, the toxicity and toxicokinetic profiles of oral treprostinil 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. Oral treprostinil has also been evaluated in reproductive developmental toxicity studies in pregnant rats and rabbits and in an in vivo rat micronucleus assay.

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, and genotoxicity. A comprehensive description of oral treprostinil, including the pharmacology, toxicology, and clinical studies completed to date, may be found in the current Investigator's Brochure.

Segment I, II, and III studies have been completed in rats, and a Segment II study has been completed in rabbits. No adverse effects for fetal viability/growth and fetal development (teratogenicity) were seen in rats at or below 20 mg/kg/day or in rabbits at or below 0.5 mg/kg/day. At high doses, teratogenic effects of oral treprostinil were observed in rabbits.

Findings included increased fetal incidence of external, soft tissue, and skeletal malformations. Initial parent generation female rats receiving 10 mg/kg/day had decreased food consumption and body weights during gestation, increased duration of gestation, slight decreases in the viability and number of pups per litter, and pups with decreased mean neonatal body weights.

A 6-month carcinogenicity study in mice with oral treprostinil administered at daily oral doses of 3, 7.5, and 15 mg/kg in females and 5, 10, and 20 mg/kg in males for 26 weeks did not demonstrate increases in the incidence of neoplastic lesions. A 2-year rat carcinogenicity study demonstrated that daily administration of oral treprostinil does not have carcinogenic potential.

A Good Laboratory Practices (GLP) cardiovascular safety pharmacology study to evaluate diethanolamine effects, independent of treprostinil, on cardiovascular function in telemetered dogs was conducted. Data support that 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 (ECG) 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

The most frequent adverse events (AEs) associated with Remodulin in clinical studies of subjects 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 subject population, was consistent with the profile noted in the controlled studies. To date, over 17,000 subjects have been exposed to Remodulin. This number includes subjects who have received single administration to subjects receiving continuous infusion for greater than 15 years.

Oral treprostinil has been administered to approximately 2100 subjects in Phase 1 to 3 clinical studies. Oral treprostinil doses of up to 3 mg twice daily (BID) have been administered to healthy volunteers, and subjects with PAH have received up to 27.5 mg 3 times daily (TID) in the ongoing Phase 2 to 3 development program. The average exposure is approximately 2 years; the longest exposure is approximately 8 years.

The absolute bioavailability of the oral treprostinil 1-mg tablet is 17.6%. Following administration, treprostinil diethanolamine is widely distributed. Treprostinil is approximately 96% protein bound, with no effect on warfarin or digoxin displacement. Pharmacokinetic (PK) data (area under the plasma concentration-time curve [AUC]) indicate that Day 1 PK 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 fat, high calorie meal, has been observed to increase absorption and prolong the systemic exposure to treprostinil, contributing to the desired PK 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 oral treprostinil indicate that CYP 2C8 appears to be of major importance and CYP 2C9 of minor importance to in vivo metabolism of oral treprostinil in humans.

To date, the majority of oral treprostinil studies have been conducted with BID dosing. In an attempt to understand the PK of TID dosing, a study was conducted in healthy volunteers. In this open-label, single-center study, 19 healthy subjects received 0.5 mg TID for 7 days.

Nineteen subjects (10 females and 9 males) with a mean age of 35.2 years (range: 20 to 54 years) were enrolled. On Day 1 the mean maximal drug concentration (C_{max}) (±standard deviation [SD]) of treprostinil was 0.574±0.22 ng/mL, which occurred at a median time of 4 hours (range: 2 to 6 hours). In comparison, the Day 8 mean C_{max} (±SD) was 0.615±0.32 ng/mL and occurred at a median time of 4 hours (range: 1 to 6 hours).

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

the day. 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.

Sixteen AEs occurred in 7 subjects and primarily included known prostacyclin class-effect related AEs (eg, headache, diarrhea, and jaw pain).

A comprehensive description of oral treprostinil, including the pharmacology, toxicology, and clinical studies completed to date can be found in the current Investigator's Brochure.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN PULMONARY HYPERTENSION ASSOCIATED WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

Oral treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in subjects with WHO Group 1 PH (Jing 2013). It has been hypothesized that the vasodilatory effects of prostanoids may also benefit WHO Group 2 PH subjects because of the precapillary component of PH due to left heart disease, which has been demonstrated in clinical studies (Hussain 2016). A study with 44 subjects with PH associated with HFpEF given sildenafil or placebo for 12 months found an increase in pulmonary arteriolar resistance (+0.69 Wood units, $p<0.01$) with stable pulmonary capillary wedge pressure (PCWP) in the placebo group, suggesting that changes in pulmonary pressure are also due to vascular dysfunction and not solely the transmission of backward pressures caused by LV diastolic dysfunction (Guazzi 2011). Another study followed 244 HFpEF subjects over 3 years to assess the severity of PH in HFpEF subjects versus hypertension subjects without heart failure. The study found increases in pulmonary artery systolic pressure (PASP) and PCWP in both the HFpEF and control groups ($p<0.007$ for both); however, after adjusting for PCWP, PASP was still higher in the HFpEF group compared with control ($p<0.001$), suggestive of a precapillary component of PH in these subjects (Lam 2009).

There are limited data on the use of prostacyclin therapy in subjects with WHO Group 2 PH. An open-label pilot study with 33 subjects with heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] ≤30%) found that epoprostenol plus

conventional therapy resulted in improvements in 6-Minute Walk Distance (6MWD) after 12 weeks when compared with conventional therapy alone (+72 meters in epoprostenol versus -39 meters in the control, p=0.033) (Sueta 1995). However, the larger scale mortality study (the FIRST study) was terminated early due to a trend toward increased mortality in subjects treated with epoprostenol. It is important to note that subjects enrolled in this study were New York Heart Association Class IIIB to IV and severely symptomatic at maximum dosages of conventional heart failure therapies. Additionally, subjects in the epoprostenol group had a higher baseline PCWP compared with the control group, thus it is unknown if the mortality trend was a result of the study drug itself or due to increased severity and progression of heart disease. Despite the mortality trend, epoprostenol did produce a significant decrease in pulmonary artery pressure mean (PAPm), PCWP, and pulmonary vascular resistance (PVR) ($p<0.01$) (Califf 1997). The results of other small studies in HFrEF subjects have been positive. A small observational study with 45 subjects with HFrEF (LVEF ≤35%) and PH showed improvements in PAPm (57.7 to 40.8 mmHg; $p<0.001$) and a trend towards increased survival (72.7% with prostaglandin E1 versus 56% in the control) after 36 months of intermittent infusions with prostaglandin E1 compared with conventional heart failure therapy (Serra 2011). When considering HFpEF subjects specifically, 1 prospective case study in HFpEF (LVEF >50%) subjects with PH showed a reduction in PAPm after both the first (-7.0 mmHg; p=0.005) and second doses (-4.7 mmHg; p=0.021) of inhaled iloprost (Grossman 2015).

There has also been positive data for the use of other vasodilators in WHO Group 2 PH subjects. A randomized, placebo-controlled study with sildenafil (a phosphodiesterase type 5 inhibitor) in HFpEF subjects (LVEF ≥50%) showed improvements in PAPm (20.8 mmHg in sildenafil versus 39.6 mmHg in placebo, $p<0.01$), PCWP (17.8 versus 22.2 mmHg, respectively; $p<0.01$), and quality of life after 12 months (Guazzi 2011). Sildenafil has also shown benefit in HFrEF (LVEF <40%) subjects. In another randomized, placebo-controlled study, treatment with sildenafil for 12 weeks resulted in improvements in exercise capacity (change in 6MWD 29 meters greater in sildenafil group; p=0.047) and quality of life (Lewis 2007). A meta-analysis including studies with HFrEF subjects found that sildenafil reduced

PAPm ($p<0.05$) and PVR ($p<0.00001$), increased exercise capacity measured as peak maximal oxygen consumption ($p<0.00001$), and improved quality of life (Wu 2014).

The guanylate cyclase stimulator, riociguat, has also been shown to be well tolerated in WHO Group 2 PH subjects and improves some hemodynamic measurements; however, riociguat has not shown reductions in PAPm. A randomized, double-blind, placebo-controlled study in HFrEF (LVEF ≤40%) subjects showed improvements in cardiac index (+0.4 L/min/m^2, $p=0.0001$), stroke volume index (+5.2 mL/m^2; $p=0.0018$), quality of life ($p=0.0002$), and reductions in PVR ($p=0.03$) with riociguat (Bonderman 2013). Similarly, riociguat was well tolerated and increased stroke volume (+9 mL, $p=0.04$) in HFpEF subjects (LVEF >50%) when compared with placebo (Bonderman 2014).

When considering endothelin receptor antagonists (ERAs), studies with bosentan have failed to show benefit in subjects with HFrEF (Packer 2005, Kalra 2002, Kaluski 2008). Studies are ongoing to investigate the potential benefit of macitentan and bosentan in HFpEF subjects (NCT02070991 and NCT00820352, respectively). These studies hypothesize that ERAs will improve exercise tolerance, hemodynamics, and quality of life.

While there are positive data for vasodilators in subjects with HFrEF associated with PH, 1 potential risk of this treatment is pulmonary edema. This has been established in 2 studies with HFrEF subjects where the decreased afterload on the right ventricle (RV) and corresponding increase in RV output with inhaled nitric oxide resulted in increased LV filling pressures, PCWP, and subsequent pulmonary edema (Loh 1994, Bocchi 1994). It is possible that pulmonary vasodilation in combination with the impaired ability of HFrEF subjects to unload the LV may have played a role in the mortality trend in the FIRST study (Califf 1997). Aside from 1 reported subject case (Boilson 2010), PH studies with vasodilators have not observed pulmonary edema in HFpEF subjects (Bonderman 2014). Unlike HFrEF subjects, HFpEF subjects have preserved systolic function and the ability to increase cardiac output in response to increases in blood volume. This pathophysiologic response, along with recent data, suggest that treprostinil can be safely administered in subjects with WHO Group 2 HFpEF.

Additionally, HFrEF has been extensively studied and the treatment guidelines are well established given the availability of multiple therapies with proven survival benefit. Conversely, no therapies have shown a reduction in mortality in HFpEF subjects, and very few have shown clinical improvement. Given that the prevalence of HFpEF is increasing and its outcome is similar to that of HFrEF, new therapies are needed to treat this disease (Ponikowski 2016). Studies have established a precapillary component of PH associated with HFpEF; thus, modulation of endothelial dysfunction via the prostacyclin pathway represents a therapeutic target with potential clinical benefit (Guazzi 2011, Lam 2009).

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that oral treprostinil will improve exercise capacity after 24 weeks of therapy as compared with placebo when administered to subjects with PH associated with HFpEF.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the effect of oral treprostinil compared with placebo on change in exercise capacity as measured by change in 6MWD from Baseline to Week 24 in subjects with PH associated with HFpEF.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to assess the effect of oral treprostinil compared with placebo on the following:

- Change in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels from Baseline to Week 24
- Time to the first clinical worsening event where clinical worsening is defined by at least 1 of the following:
  - Hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or heart failure)
  - Outpatient administration of IV diuretics
  - Decrease in 6MWD >15% from Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study) at 2 consecutive visits on different days (except at Week 24)

  - Death (all causes)
- Change in WHO Functional Class from Baseline to Week 24

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are to assess the effect of oral treprostinil compared with placebo on the following:

- Change in 6MWD from Baseline to Weeks 6, 12, and 18
- Change in Borg dyspnea score from Baseline to Weeks 6, 12, 18, and 24
- Change in NT-proBNP levels from Baseline to Week 12
- Change in glycated hemoglobin (HbA1c) from Baseline to Week 24
- Change in WHO Functional Class from Baseline to Weeks 6, 12, and 18
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from Baseline to Week 24
- Optional evaluation of biomarkers (specific targets to be determined) from Baseline to Week 24
- Optional evaluation of pharmacogenomics

2.4 SAFETY ENDPOINTS

To evaluate the effect of oral treprostinil on the following parameters:

- AEs
- Clinical laboratory parameters
- Physical examinations
- Assessment of heart failure signs and symptoms with vital signs
- ECGs
- Echocardiograms (ECHOs)
- Hospitalizations due to cardiopulmonary indication
- Worsening heart failure as demonstrated by outpatient administration of IV diuretics

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled study in subjects with WHO Group 2 PH associated with HFpEF. Subjects will be assessed during Screening to determine eligibility for the study. Confirmation of eligibility criteria in Section 4 will be

confirmed during the Baseline Visit prior to randomization. Once randomized, subjects will be dispensed study drug and will take the initial dose of study drug at the study site on the day of randomization. The subject will return to the study site for visits scheduled at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable; see Table 3-1). If a subject completes the 24-week treatment period on study drug, they will be permitted to enter the open-label extension study (Study TDE-HF-302). If a subject prematurely discontinues the study for any reason, has the study blind broken, or permanently discontinues study drug, they will not be permitted to enter the open-label extension study.

At each scheduled visit after randomization, subjects will undergo the following efficacy assessments: exercise capacity as measured by the 6-Minute Walk Test (6MWT) and Borg dyspnea score, clinical worsening, and WHO Functional Class. At every scheduled protocol visit following randomization, measurement of exercise capacity via the 6MWT will occur 3 to 6 hours after the most recent dose of study drug. This 3 to 6 hour time window does not apply to subjects who have permanently discontinued study drug and have remained in the study, or those that are currently on a prescribed zero dose from the Investigator. Serum samples will also be collected for measurement of NT-proBNP at Baseline, Week 12, and Week 24, and the Study Drug Termination Visit (if applicable). The KCCQ will be collected at Baseline and Week 24, and the Study Drug Termination Visit (if applicable). See Table 3-1 for the overall schedule of time and events.

Safety will be assessed by vital signs, physical examination, assessment of heart failure signs and symptoms, pregnancy testing, AEs, and clinical laboratory parameters. Subjects will undergo a 12-lead ECG at Baseline and Week 24, and the Study Drug Termination Visit (if applicable); and an ECHO during Screening (prior to randomization) and Week 24, and the Study Drug Termination Visit (if applicable).

Subjects on a chronic medication for heart failure (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blockers [ARBs], and beta blockers) must be on a stable dose for ≥30 days prior to randomization. The exception is with changes of anticoagulants and/or diuretics; these medications should not be newly started or stopped within 30 days of randomization and no healthcare provider prescribed dose change should occur within 7 days

of randomization, with the exception of the withholding of doses of anticoagulants for the conduct of the right heart catheterization (RHC) when required.

Subjects will receive their first dose of study drug (0.125 mg) at the study site on the day of randomization. Dosing of study drug will be continued at 0.125 mg TID (every 6 to 8 hours) with food, up to an initial maximum dose of 2 mg TID. Based on the approval by the independent Data Monitoring Committee (DMC), the dose will be slowly titrated throughout the study up to a maximum of 4 mg and then 6 mg TID, as safety data permit, in an effort to reach a tolerated dose that provides clinical benefit.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Time and Events

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening and Baseline Visit[a]	Treatment Phase				
Study Week				**Week 6[b]**	**Week 12[b]**	**Week 18[b]**	**Study Drug Termination (if applicable)**	**Week 24[b]**
Study day	-30 to -1	1	1	43	85	127		169
Informed consent	X		X					
Subject eligibility[c]	X	X	X					
Medical history with PH history, HF history, and demographics	X		X					
KCCQ		X	X				X	X
Physical examination	X		X				X	X
Assessment of heart failure signs and symptoms with vital signs[d]	X	X	X	X	X	X	X	X
12-lead ECG		X	X				X	X
ECHO[e]	X---	---X	X				X	X
WHO Functional Class		X	X	X	X	X	X	X
Clinical laboratory assessments	X	X	X		X		X	X
NT-proBNP[f]		X	X		X		X	X
HbA1c		X	X				X	X
Urine pregnancy test[g]	X	X	X	X	X	X	X	X
Pre-Baseline Review Form	X		X					
6MWT and Borg dyspnea score[h]	X	X	X	X	X	X	X	X
Randomization		X	X					
Dosing instructions/ dosing/accountability		X[l]	X[l]	X	X	X	X	X

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening and Baseline Visit[a]	Treatment Phase				
Study Week				**Week 6[b]**	**Week 12[b]**	**Week 18[b]**	**Study Drug Termination (if applicable)**	**Week 24[b]**
Weekly telephone/email contact[i]		X--	X--	--X--	--X--	--X--	--X	--X
Adverse events[j]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Concomitant medications	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Assessment of clinical worsening[k]		X--	--X--	--X--	--X--	--X--	--X	--X
Survival status							X[m]	X[m]
Blood sample for biomarker evaluation (Optional)[n]		X	X				X[p]	X[p]
Urine sample for biomarker evaluation (Optional)[n]		X	X				X[p]	X[p]
Pharmacogenomic Sample (Optional)[o]		X	X				X[p]	X[p]

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test; AE, adverse event; ECG, electrocardiogram; ECHO, echocardiogram; eCRF, electronic case report form; HF, heart failure; IV, intravenous(ly); KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; SAE, serious adverse event; TID, 3 times daily; WHO, World Health Organization

[a] Screening Visit assessments can occur up to 30 days prior to randomization and after informed consent has been obtained. Baseline assessments can occur up to 48 hours prior to the first dose of study drug to allow for scheduling of all activities; however, the Baseline 6MWT must be performed prior to, but on the same day as, the first dose of study drug. Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug.

[b] The visit window is ±5 days from the projected visit date.

[c] For the Screening and Baseline visits, the subject must be evaluated for and meet all inclusion criteria and not meet any exclusion criteria.

[d] Refer to Appendix 15.7 for the assessments of heart failure signs and symptoms to be completed. Vital signs must be collected after 5 minutes of rest (seated); no other measurements or procedures should be performed during this 5-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, then they should be obtained after a minimum 30-minute recovery from the 6MWT.

[e] ECHO must be completed during Screening (prior to randomization) and assessed locally for LVEF. It should also be conducted in accordance with the manual provided by the ECHO core lab and uploaded to the central imaging center.

[f] Blood for NT-proBNP assessments must be drawn prior to conducting the 6MWT and will occur prior to the first dose of study drug at Baseline (or as part of the Baseline Visit assessment if the Screening and Baseline visits are combined).

[g] For females of childbearing potential. Urine pregnancy test at Screening and Baseline to be completed prior to randomization.

[h] If the subject has not previously undergone a 6MWT at the study site on the study-designated course, a practice test must be conducted at the Screening Visit and must precede the Baseline 6MWT by at least 1 day. The Baseline 6MWT must be performed on the same day as and precede the first dose of study drug. All 6MWTs

following randomization must be conducted 3 to 6 hours after the most recent dose of study drug. Prior to the start of each 6MWT, the subject should rest (seated) for at least 10 minutes. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate and mode of oxygen therapy at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable. The Borg dyspnea score should be conducted immediately following the 6MWT.

[i] At least weekly telephone contact is required throughout the study to monitor study drug compliance, AEs, use of concomitant medications, occurrence of clinical worsening, signs and symptoms of disease, and to make decisions regarding dose titration (may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or at the study site for clinically significant AEs or other emergent issues.

[j] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 24 study assessments have been completed, and should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit.

[k] Clinical worsening will be assessed continuously from randomization to Week 24 or Study Drug Termination until any of the following criteria are met: hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or heart failure), administration of outpatient IV diuretics, decrease in 6MWD >15% from Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study) at 2 consecutive visits on different days (except Week 24), or death (all causes). Assessment for clinical worsening should continue for 7 days after the final dose of study drug if a subject permanently discontinues study drug during the treatment phase.

[l] Once all entry criteria have been met and all Baseline assessments completed, the first dose of study drug (0.125 mg) will be administered at the study site. Study drug dosing will continue at 0.125 mg TID (every 6 to 8 hours) with food, up to an initial maximum dose of 2 mg TID.

[m] Subjects who discontinue the study and do not enter Study TDE-HF-302 will be contacted approximately 30 days (±5 days) after study drug discontinuation to confirm their survival status.

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

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

[p] Subjects who consent to the optional pharmacogenomic and/or biomarker samples and discontinue study drug prior to Week 24 should provide samples at the Study Drug Termination Visit and the Week 24 Visit.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 6-Minute Walk Test

The intent of the 6MWT is to evaluate exercise capacity associated with carrying out activities of daily living. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements described in Appendix 15.1 (ATS 2002, Holland 2014). Prior to the start of each 6MWT, the subject should rest (seated) for at least 10 minutes. The 6MWT instructions provided in Appendix 15.1 apply to the practice walk (if applicable), the walks conducted at Baseline, Weeks 6, 12, 18, and 24, and any repeat 6MWT done for the purpose of this study.

3.3.1.1.1 Practice 6-Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course intended for use during the study. If no previous 6MWT has been performed at the study site on the study-designated course, a practice 6MWT must be conducted at the Screening Visit and must precede the Baseline 6MWT by at least 1 day for applicable subjects.

3.3.1.1.2 Baseline 6-Minute Walk Test

A Baseline 6MWT must be performed prior to initiation of study drug and should be conducted no more than 48 hours prior to randomization. After the Baseline 6MWT has been conducted and the subject is ready for randomization, the study site will enter the subject's 6MWD into an interactive voice or web response system (IVRS/IWRS). The IVRS/IWRS will confirm to study site personnel the subject's eligibility to participate in the study based on 6MWD, and if the subject is eligible, randomize them into a treatment group and allocate appropriate study drug.

The Baseline 6MWT must be conducted free of any unusual or extenuating circumstances (eg, intercurrent illness other than that under study, ankle or knee sprains, unusual pain affecting the lower limbs, respiratory infection, etc). If there is any unusual or extenuating circumstance at Baseline, the visit should be postponed to allow adequate time for the recovery of the subject. If the 30-day Screening phase is exceeded by allowing the subject to

recover, the subject can be re-screened at a later time when the unusual or extenuating circumstance is adequately resolved so as to not impact the results of the Baseline 6MWT.

NOTE: The Baseline 6MWT (not the practice 6MWT) will determine the subject's eligibility to participate in the study.

3.3.1.1.3 Treatment 6-Minute Walk Tests

The 6MWTs will be conducted at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable). The 6MWT should be conducted 3 to 6 hours following the most recent dose of study drug. This 3 to 6 hour time window does not apply to subjects who have permanently discontinued study drug and have remained in the study, or those that are currently on a prescribed zero dose from the Investigator. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate and mode of oxygen therapy at all subsequent 6MWT assessments; any changes in oxygen therapy administration should be noted in the electronic Case Report Form (eCRF). In addition, subjects receiving pulmonary or cardiac rehabilitation prior to study entry should continue on the same schedule up to and including Week 24. Pulmonary or cardiac rehabilitation may not be added to, or discontinued from, a subject's regimen between 4 weeks before randomization and Week 24. Subjects utilizing a walker or cane for stability must also use a walker or cane at every 6MWT during the study. Additional 6MWTs may be conducted as appropriate throughout the course of the study for the purposes of evaluating the clinical worsening status.

Each 6MWT conducted after randomization should be documented and compared with the subject's Baseline 6MWD. If a subject has a decrease of more than 15% in 6MWD compared with Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study), a second confirmatory 6MWT should be performed on a different day to assess for clinical worsening. Note that the first 6MWT distance should be counted as the one determining the clinical worsening event, rather than the confirmatory 6MWT. Confirmatory 6MWTs are required for every visit except the Week 24 Visit where a decrease of more than 15% (or the subject is too ill to walk, and the cause is directly related to the disease under study) in 6MWD would be considered a clinical worsening event. Confirmatory 6MWTs must be consecutive and should be conducted within 30 days of the initial qualifying decrease

in 6MWD; however, confirmatory 6MWTs occurring outside of this window will still be considered to have met the definition of clinical worsening. If the second consecutive 6MWT also shows more than a 15% decrease in 6MWD as compared with Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study), the subject will meet the definition of clinical worsening. The subject will remain in the study and continue dosing with study drug until the Week 24 Visit, even if clinical worsening has been met. Details regarding the conduct of the 6MWT are described in Appendix 15.1.

3.3.1.2 Borg Dyspnea Score

The Borg dyspnea score will be assessed immediately 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 subject's WHO Functional Class (Appendix 15.2) will be assessed at Baseline prior to starting study drug and at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable).

3.3.1.4 Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-question, self-administered, health-related quality of life survey validated for heart failure that assesses physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life. Responses are arrayed on an adjectival (Likert) scale with clinically meaningful graduations between categories. It is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing items within each domain (Green 2000). This assessment will be conducted at Baseline (prior to starting study drug) and Week 24, and the Study Drug Termination Visit (if applicable). The KCCQ questionnaire is available for this study in English (US and Canada), French (Canada), and Spanish (US and Mexico). Subjects whose primary language is not English, Canadian French, or Spanish should not complete the KCCQ. Additional detail is provided in Section 10.3.4.6, and an example of the KCCQ is provided in Appendix 15.6.

3.3.1.5 Clinical Worsening

Clinical worsening will be assessed continuously from randomization until Week 24, or the Study Drug Termination Visit (if applicable). Assessment for clinical worsening should continue for 7 days after the final dose of study drug if a subject permanently discontinues study drug during the Treatment Phase. A subject may experience multiple clinical worsening events based on the 4 categories below. The first occurrence within each category will be recorded in the eCRF if multiple events are experienced by a subject (eg, if a subject receives outpatient IV diuretics on 4 different occasions throughout the study, only the first occurrence should be recorded in the eCRF. If the subject is hospitalized due to a cardiopulmonary indication, that would also be recorded as a clinical worsening event). All clinical worsening events will be reviewed by the Sponsor's Medical Monitors as part of their review of clinical data sets. Clinical worsening is defined as the occurrence of any of the following:

- Hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PH and/or heart failure)
- Outpatient administration of IV diuretics
- Decrease in 6MWD >15% from Baseline (or the subject is too ill to walk, and the cause is directly related to the disease under study) at 2 consecutive visits on different days. Confirmatory 6MWTs are required for every visit except the Week 24 Visit where a decrease of more than 15% (or the subject is too ill to walk and the cause is directly related to the disease under study) in 6MWD would be considered a clinical worsening event.
- Death (all causes)

3.3.1.6 N-Terminal Pro-brain Natriuretic Peptide

NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). NT-proBNP sample collection will occur at Baseline (prior to starting study drug), Week 12, and Week 24, and the Study Drug Termination Visit (if applicable).

3.3.2 Safety

3.3.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PH history, and physical examination will be conducted during the Screening phase. Clinically significant past or present illnesses, current prescription and nonprescription medications (including vitamins and herbal products), and a history of allergies or idiosyncratic responses to drugs should be noted in the eCRF, as required. Any significant changes to the subject's medical condition, physical examination, and concomitant medications must be documented throughout the course of the study. A complete physical examination will also be conducted at Week 24, and the Study Drug Termination Visit (if applicable).

3.3.2.2 Clinical Laboratory Tests

A central clinical laboratory will be used to standardize test results. Clinical laboratory tests will be assessed at the Screening and Baseline visits prior to starting study drug. Screening and Baseline clinical laboratory assessments can be combined into a single blood draw if all combined screening and baseline procedures are completed and all eligibility criteria are confirmed within 48 hours prior to randomization. Central laboratory data are ultimately used to qualify subjects for the study. For subjects who are well known to the Investigator and who are clinically stable, the Investigator may choose not to delay randomization at a combined Screening/Baseline Visit and may utilize local laboratory values to confirm eligibility while waiting for central laboratory confirmation. Clinical laboratory assessments will also be assessed at Weeks 12 and 24, and the Study Drug Termination Visit (if applicable). Clinical laboratory assessments and a Visit Test Schedule are displayed in Appendix 15.4.

3.3.2.3 Adverse Events

The AEs will be captured from the time the Informed Consent Form (ICF) is signed. All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study 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 study visit. Sections 9.1.1 and 9.1.2 and Appendix 15.3 provide the guidelines and definitions for recording AEs and SAEs.

Events attributable to the progression of the disease under study should only be recorded as an AE or SAE if the event is unusual with respect to intensity, frequency, duration as compared with symptoms in the subject's medical history, or if there is a reasonable possibility that the event was caused by the study drug (Table 3-2).

Table 3-2 Expected Events Attributable to the Progression of the Disease Under Study

Abdominal pain	Palpitations
Anorexia	Paroxysmal nocturnal dyspnea
Chest pain	Peripheral edema/generalized edema
Dizziness	Presyncope
Dyspnea/dyspnea on exertion	Pulmonary hypertension, exacerbation of
Exercise tolerance decreased	Left heart failure/left ventricular failure
Fatigue	Right heart failure/right ventricular failure
Hypoxia	Sudden death
Lethargy	Syncope
Loss of consciousness	Weight loss
Orthopnea	Weight gain

Note: Symptoms of right ventricular failure/right heart failure can include, but are not limited to, ascites, cyanosis, tachycardia, and other cardiac arrhythmias. The effects of pulmonary hypertension and right ventricular failure/right heart failure can include cardiac arrest and death.

3.3.2.4 12-Lead Electrocardiogram

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

3.3.2.5 Echocardiogram

Two-dimensional transthoracic ECHO examinations will be performed during Screening (prior to randomization) and Week 24, and the Study Drug Termination Visit (if applicable). The ECHO results will be uploaded and stored in a central repository. The ECHO examination performed prior to randomization will be assessed locally to ensure inclusion

criterion 4 is met. All ECHO examinations will be conducted in accordance with the manual provided by the ECHO core lab facility and uploaded to the central imaging center. The following echocardiographic parameters will be measured:

- RV fractional area change
- Tricuspid annular plane systolic excursion
- The maximal tricuspid regurgitant jet velocity
- Right atrial area
- Right atrial pressure (estimated by inferior vena cava)
- LV ejection fraction
- Left atrial volume index
- Mitral E velocity
- Mitral A velocity
- Mitral septal e' velocity
- Mitral lateral e' velocity

Additional exploratory parameters may be assessed.

3.3.2.6 Pregnancy Testing

All women of childbearing potential (WOCBP) will undergo a urine pregnancy test at Screening and Baseline prior to randomization, and at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable). A positive pregnancy test will exclude the subject from further participation in the study. Subjects who become pregnant during the study are to be discontinued from the study.

3.3.2.7 Assessment of Heart Failure Signs and Symptoms with Vital Signs

Signs and symptoms of heart failure (Appendix 15.7) will be assessed at Screening, Baseline (prior to starting study drug), and during the Treatment Phase at Weeks 6, 12, 18, and 24, and the Study Drug Termination Visit (if applicable). Data from the review of the heart failure signs and symptoms will not be included in the eCRF; however, if there are clinically significant changes in the opinion of the Investigator relative to Baseline, they should be recorded as AEs. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, then they should be obtained after a minimum 30-minute recovery from the 6MWT. Vital signs must be collected after 5 minutes of rest

(seated); no other measurements or procedures should be performed during this 5-minute period. Vital signs include blood pressure, peripheral (radial/brachial artery) heart rate, weight, and respiration rate. Height will be collected at the Baseline Visit only.

3.3.3 Pharmacogenomics

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood sample will be collected for pharmacogenomic analyses. Participation in the pharmacogenomic sampling is optional and samples will be collected at Baseline, the Study Drug Termination Visit (if appropriate), and Week 24 as noted in the Overall Schedule of Time and Events (see Table 3-1).

Samples will be stored, and analyses may be performed on genetic variants or gene expression patterns thought to play a role in pulmonary hypertension to evaluate their association with observed response to prostacyclin therapy including oral treprostinil.

3.3.4 Biomarkers

Samples will be collected for potential biomarker research where local regulations allow. Samples may be used for research on the drug target, disease process, pathways associated with pulmonary hypertension, mechanism of action of oral treprostinil, and/or research method or in validating diagnostic tools or assay(s) related to pulmonary hypertension. Participation in the biomarker sampling is optional and serum and urine samples will be collected at Baseline, the Study Drug Termination Visit (if appropriate), and Week 24 as noted in the Overall Schedule of Time and Events (see Table 3-1).

3.4 NUMBER OF CENTERS

This is a multicenter study with approximately 100 study sites in the US, Canada, and Mexico participating.

3.5 NUMBER OF SUBJECTS

Approximately 310 subjects will be randomized (1:1 oral treprostinil to placebo) across all study sites.

3.6 ESTIMATED STUDY DURATION

The maximum length of participation is approximately 28 weeks. This includes an up to 30-day Screening phase and the 24 weeks of treatment. Subjects who permanently discontinue study drug (eg, due to an AE) prior to Week 24 will be asked to complete a Study Drug Termination Visit and remain in the study through Week 24 and complete study assessments off treatment. The study will enroll until approximately 310 subjects are randomized. Subjects who permanently discontinue study drug and do not enter Study TDE-HF-302 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 ongoing AEs/SAEs (see Section 9 for additional details).

4 SUBJECT ELIGIBILITY

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

4.1 INCLUSION CRITERIA

1. The subject voluntarily gives informed consent to participate in the study.
2. The subject is 18 to 85 years of age (inclusive) at Screening (ie, date of providing written informed consent).
3. A subject can qualify if they have undergone a RHC within 180 days of Baseline and either of the following conditions (regular criterion or fluid challenge criterion) are met:

   Regular criterion:

   a. A PAPm ≥25 mmHg
   b. A PCWP >15 mmHg but ≤30 mmHg. In cases where a PCWP is not available or deemed unreliable, a left ventricular end-diastolic pressure (LVEDP) obtained within the 180-day window may be used. Note that a subject would be eligible to

participate in the trial if they have a PAPm ≥25 mmHg, a PVR ≥3 wood units, and a PCWP ≤15 mmHg from a RHC conducted during the Screening period if they had a PCWP >15 mmHg (with no upper limit) associated with a diagnosis of HFpEF on the preceding RHC (done within 180 days of Baseline).

c. A PVR of ≥3.0 Wood units (≥240 dynes*s/cm^5) calculated using thermodilution or Fick technique.

Fluid challenge criterion:

a. A PAPm ≥25 mmHg
b. A positive fluid challenge, namely a PCWP ≥16 mmHg after ~500 ml saline infused via IV over approximately 5 minutes.
c. A PVR of ≥3.0 Wood units (≥240 dynes*s/cm^5) calculated using thermodilution or Fick technique
d. 3 or more of the following risk factors for PH associated with HFpEF:
   i. Hypertension
   ii. Type 2 diabetes mellitus
   iii. Hyperlipidemia
   iv. Atrial fibrillation
   v. Age >65 years old
   vi. Sleep apnea
   vii. Left atrial volume index >32 ml/m^2 (transthoracic echocardiogram)
   viii. Body mass index >30 kg/m^2

4. The subject has a diagnosis of heart failure with a LVEF ≥45% by ECHO completed during Screening (prior to randomization).
5. The subject's baseline 6MWD must be at least 150 meters.
6. The subject has pulmonary function tests conducted within 6 months of Screening or during the Screening phase to confirm the following:
   a. Total lung capacity is ≥ 60% of the predicted value.
   b. Forced expiratory volume at 1 second (FEV_1) is ≥50% of the predicted value.
   c. Diffusing capacity of the lungs for carbon monoxide (DLCO) is ≥40% of the predicted value (unadjusted, or adjusted for alveolar volume).
7. Subjects on a chronic medication for heart failure (eg, ACE inhibitors, ARBs, and beta blockers) must be on a stable dose for ≥30 days prior to randomization. The exception is with changes of anticoagulants and/or diuretics; these medications should not be newly started or stopped within 30 days of randomization and no healthcare provider prescribed dose change should occur within 7 days of randomization, with the exception of the withholding of doses of anticoagulants for the conduct of the RHC when required.
8. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing, and likely to be cooperative with protocol requirements, including attending all study visits.

9. WOCBP 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). 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 drug. 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 WOCBP, a negative urine pregnancy test is required at Screening and Baseline prior to initiating study drug. Male subjects with a partner of childbearing potential must use a condom during the length of the study, and for at least 48 hours after discontinuing study drug.
10. Subjects on chronic medications (eg, inhaled corticosteroids, long-acting beta$_2$-adrenergic agonist, long-acting muscarinic antagonists, combination inhaled drugs, anti-inflammatory drugs, oral/parenteral corticosteroids, or biologic agents) for any underlying respiratory condition must be on a stable dose for ≥30 days prior to randomization.

4.2 EXCLUSION CRITERIA

1. The subject is pregnant or lactating.
2. In the opinion of the Principal Investigator, the subject has a primary diagnosis of PH other than WHO Group 2 PH.
3. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation of therapy or inability to effectively titrate that therapy.
4. The subject has received PAH therapies, including prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), nonprostanoid IP receptor agonist (selexipag), ERA, or soluble guanylate cyclase stimulator, within 30 days of randomization. Chronic use of an approved phosphodiesterase type 5 inhibitor (PDE5-I) is allowed as long as the subject has been on a stable dose for at least 90 days prior to randomization and has had an RHC confirming the parameters necessary for inclusion in the study after being on a stable PDE5-I dose for at least 30 days. If the Investigator does not intend to keep a subject on their PDE5-I therapy, it must be stopped at least 30 days prior to randomization. Intermittent use of a PDE5-I (≤3 times per week) to treat erectile dysfunction is permitted.
5. The subject has been hospitalized for a cardiopulmonary indication within 30 days of randomization.
6. The subject had a myocardial infarction within 90 days of randomization.
7. The subject had cardiac resynchronization therapy within 90 days of randomization or anticipated resynchronization therapy during the study treatment period.

8. The subject has liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than 3 times the upper limit of normal at Screening, clinically significant liver disease/dysfunction per Investigator's clinical judgement, known Child-Pugh Class C hepatic disease (see Appendix 15.5), or noncirrhotic portal hypertension.
9. The subject has uncontrolled systemic hypertension, defined as a systolic blood pressure >160 mmHg or a diastolic blood pressure >110 mmHg at Baseline.
10. The subject has a systolic blood pressure <100 mmHg at Baseline.
11. The subject has a resting heart rate >100 beats per minute at Baseline.
12. The subject has known genetic hypertrophic cardiomyopathy.
13. The subject has sarcoidosis or cardiac amyloidosis.
14. The subject has a known history of any LVEF less than 40% by ECHO within 3 years of randomization. Note: a transient decline in LVEF below 40% that occurred and recovered more than 6 months before the start of Screening and was associated with an acute intercurrent condition (eg, atrial fibrillation) is allowed.
15. The subject has hemodynamically significant valvular heart disease as determined by the Investigator, including:
    - Greater than mild aortic and/or mitral stenosis
    - Severe mitral and/or aortic regurgitation (>Grade 3)
16. The subject has a body mass index >45 kg/m^2.
17. The subject has any musculoskeletal disorder (eg, arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), or has any other condition that would likely be the primary limit to ambulation as opposed to the disease under study.
18. The subject has end-stage renal disease requiring/receiving dialysis.
19. The subject has used any investigational drug/device, or participated in any investigational study, within 30 days prior to the first dose of study drug.

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

All subjects on a chronic medication for heart failure (eg, ACE inhibitors, ARBs, and beta blockers) must be on a stable dose for ≥30 days prior to randomization. The exception is with changes of anticoagulants and/or diuretics; these medications should not be newly started or stopped within 30 days of randomization and no healthcare provider prescribed dose change should occur within 7 days of randomization, with the exception of the withholding of doses of anticoagulants for the conduct of the RHC when required. After randomization, additions, deletions, and dose changes of any heart failure therapy may occur if the Investigator determines it is medically necessary; however, every attempt should be made to minimize

changes to background heart failure (HF) therapy. If changes to conventional heart failure therapies are made, study drug should be continued as per protocol.

Subjects who are chronically using an approved PDE5-I prior to entry into the study must have been on a stable dose for at least 90 days prior to randomization and should remain on a stable dose throughout the study. If the Investigator does not intend to keep a subject on their PDE5-I therapy, it must be stopped at least 30 days prior to randomization. If a subject is on intermittent doses of a PDE5-I to treat erectile dysfunction, they cannot take more than 3 doses per week.

All subjects receiving chronic medications (eg, inhaled corticosteroids, long-acting $beta_2$-adrenergic agonist, long-acting muscarinic antagonists, combination inhaled drugs, anti-inflammatory drugs, oral/parenteral corticosteroids, or biologic agents) for any underlying respiratory condition must be on a stable dose for at least 30 days prior to randomization.

For the purposes of the 6MWT, if the subject was assessed at Baseline using oxygen therapy, then all future 6MWTs during the study must be conducted with the same oxygen flow rate and mode of administration. Conversely, if the subject was assessed at Baseline without oxygen therapy, then all future 6MWTs during the study should be conducted without oxygen therapy unless it would represent a safety risk to the subject. Any changes to oxygen therapy relative to Baseline when conducting the 6MWT will be considered an unusual circumstance for eCRF completion purposes.

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

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Eligible subjects will be randomly allocated 1:1 to receive either oral treprostinil or placebo at randomization. During the Screening phase, a screening number will be assigned using an

electronic data capture system to identify individual subject data until the subject is randomized. Upon randomization, each subject will be assigned a new unique study subject number via the IVRS/IWRS. The IVRS/IWRS will also be responsible for allocation of all study drug.

5.2 RANDOMIZATION

The study will be randomized 1:1 oral treprostinil to placebo. All subjects will be randomly allocated to receive oral treprostinil or placebo through the IVRS/IWRS using a centrally administered randomization. The randomization will be stratified by Baseline 6MWD (less than or equal to 350 meters and greater than 350 meters).

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

5.3 BLINDING

The Investigator, study site personnel, subject, and Sponsor will not be aware of the treatment allocation. All clinical study material will be provided as blinded study drug. See Section 6.2 for the procedure for unblinding subjects at the end of study to determine appropriate starting dose for the open-label study (Study TDE-HF-302).

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

The oral treprostinil tablets are SR osmotic tablets. Active treatment is oral treprostinil tablets provided as 0.125-, 0.25-, 1-, and 2.5-mg strengths. The 0.125-, 0.25-, 1-, and 2.5-mg tablets are colored blue, green, yellow, and pink, respectively. The formulation contains pharmaceutically acceptable excipients used in other approved drug products. Placebo tablets are identical in size, shape, and color to the respective oral treprostinil tablets.

Once all entry criteria have been met and treatment randomly assigned by IVRS/IWRS, the first dose of study drug (0.125 mg) should be taken by the subject immediately after (approximately 10 minutes) consuming food at the study site on the day of randomization. Oral dosing of study drug will be continued at 0.125 mg TID (every 6 to 8 hours) immediately after (approximately 10 minutes) the subject consumes food. Subjects must be instructed to

take the appropriate number of tablets based upon their prescribed dose. Each dose of study drug can be upwardly adjusted by a maximum of 0.125-mg increments as clinically indicated and tolerated. Throughout the course of the study, dose increases can occur in 0.125-mg increments every 72 hours (9 consecutive doses) as indicated at the discretion of the Investigator up to an initial maximum allowable dose of 2 mg TID. If necessary, dose titration can occur less frequently than every 9 doses. The anticipated maximum allowed dose during the study will be 6 mg TID based on recommendations from the independent DMC. The DMC will meet after approximately 10, 30, 60, 100, and 200 subjects have been enrolled in the study, or on an ad hoc basis per request of the independent DMC, as necessary. Enrollment will not be stopped during the DMC reviews; however, subjects may not progress to the next highest maximum dose level until the DMC provides their review of the data. Any decision impacting the maximum dose will be relayed to study sites following the DMC meeting. Note that sudden dose escalations or reductions may lead to intolerable AEs or worsening of PH, and gradual dose escalations or reductions are recommended to reduce risk to subjects.

Doses of study drug should continue to be increased in the absence of dose-limiting drug-related AEs to ensure that each subject receives the optimal clinical dose throughout the study. Table 6-1 provides an anticipated maximum dose of study drug that can be obtained based on DMC review and approval, notwithstanding any AEs that limit dose escalation.

Table 6-1 Anticipated Maximum Dose Ranges Based on DMC Review and Approval

Approximate Number of Subjects	Maximum Dose
1 to 10	2 mg TID
11 to 30	4 mg TID
31 and above	6 mg TID

DMC, Data Monitoring Committee; TID, 3 times daily

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Each dose of study drug is not required to be the same during titration. For example, doses of 1.125 mg in the morning, 1.125 mg in the afternoon, and 1.25 mg in the evening, are acceptable during titration. The maximal difference between the lowest dose and the highest doses cannot exceed 0.125mg.

Weekly telephone calls or emails between scheduled visits (eg, Weeks 1, 2, 3, 4, and 5 between randomization and Week 6) up to Week 24, and the Study Drug Termination Visit (if applicable) are to be made between study site personnel and the subject to monitor study drug compliance, AEs, signs and symptoms of disease, use of concomitant medications, occurrence of clinical worsening, and to make decisions regarding dose titration. More frequent telephone calls may be necessary depending on the frequency of dose titration and to manage AEs or signs and symptoms of disease. If dose titration is considered appropriate, study site personnel will instruct the subject to modify their dose. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or at the study site for clinically significant AEs or other emergent issues.

Study drug dose should be recorded at each study visit 6MWT between Week 6 and Week 24. Dose changes between Baseline and Week 24 will be recorded in source documentation and the subject's eCRF by study site personnel. If it becomes necessary for a subject to modify their dose (eg, due to an AE) without prior instructions from study site personnel, the subject should be instructed to contact the study site as soon as possible and report any dose changes to study site personnel for updating in source documentation and the eCRF, as appropriate. Subjects must not make-up or double-up on missed doses of study drug. If dosing is interrupted for longer than 24 hours, consideration should be given to gradually retitrate the subject's dose to the last dose administered prior to the dose interruption. In the event of a planned, short-term interruption for subjects unable to take oral medications during the study, study sites should contact the United Therapeutics Medical Monitor to discuss dosing options.

In the event a subject is required to be permanently discontinued from study drug (eg, adverse event, requirement for the addition of a prohibited medication, or the subject wishes to withdraw from further participation in the study), the Investigator should conduct the Study Drug Termination Visit assessments (see Table 3-1) and then gradually down-titrate the study drug, taking into consideration the subject's clinical condition, current study drug dosing regimen, and previous clinical response to study drug. Subjects who terminate study

drug early will be asked to complete all remaining study visits in addition to the Study Drug Termination Visit.

Throughout the course of the study, the dose of study drug can be increased at the discretion of the Investigator up to an initial maximum allowable dose of 2 mg TID prior to a DMC-approved dose escalation. Dose escalation may be made less frequently or temporarily suspended if a subject experiences an intolerable AE that may worsen as a result of an increase in study drug dose. If an AE remains intolerable, the Investigator may decrease the dose of study drug. In the event of continued intolerable AEs, further 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. If the subject is still experiencing an intolerable AE, then the Investigator may temporarily or permanently withdraw the subject from study drug. Following temporary discontinuation of study drug, all attempts should be made to re-initiate study drug in affected subjects. Subjects should be restarted on study drug at a reduced dose or at 0.125 mg TID depending on the clinical condition of the subject, the subject's previous response to study drug, the dose at the time of discontinuation, and the duration of temporary discontinuation from study drug. Following restart of study drug, all efforts should be made to increase the dose until the desired clinical improvement in the subject's symptoms of PH occurs, so long as the maximum allowable dose determined by the DMC is not surpassed.

Subjects that complete through Week 24 on study drug and do not roll over to the TDE-HF-302 study shall be provided enough study drug for down-titration and discontinuation of dosing from either their remaining study drug supply that was provided at Week 18 and/or via an unscheduled call to the IVRS/IWRS during Week 24 (prior to the study completion call). Subjects should not down-titrate their dose of study drug until after the Week 24 Visit has been completed. Following completion of the Week 24 Visit, subjects should down-titrate until a zero dose is achieved. As needed, site personnel should maintain at least weekly

contact via phone or email until a zero dose is achieved and ensure the return of all unused study drug to the study site.

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

6.1.1 Dosing of Study Drug in Relation to Meals

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

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

6.1.2 Dosing and Administration of Concomitant Medications

All subjects on a chronic medication for heart failure (eg, ACE inhibitors, ARBs, and beta blockers) must be on a stable dose for ≥30 days prior to randomization (see Section 4.3.1). The exception is with changes of anticoagulants and/or diuretics; these medications should not be newly started or stopped within 30 days of randomization and no healthcare practitioner prescribed dose change should occur within 7 days of randomization with the exception of the withholding of doses of anticoagulants for the conduct of the RHC when required. After randomization, additions, deletions, and dose changes of any background therapy as above may occur if the Investigator determines it is medically necessary; however, every attempt should be made to minimize changes to background therapies. If changes to background medications are made, study drug should be continued as per protocol.

6.1.3 Prohibited Medications

Subjects must not be receiving PAH therapies, including prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), nonprostanoid IP receptor agonist (selexipag), ERA, or soluble guanylate cyclase stimulator within 30 days of randomization through the permanent discontinuation of study drug or study termination. The exception is that intermittent use of a PDE5-I (≤3 times per week) to treat erectile dysfunction is permitted, as well as chronic use of an approved PDE5-I that was initiated at least 90 days prior to randomization. PDE5-I therapy is not to be initiated within 90 days of randomization or after randomization through the permanent discontinuation of study drug or study termination. If the Investigator feels that starting an approved PAH therapy is clinically necessary during the course of the study, a Study Drug Termination Visit should be scheduled and the subject should be withdrawn from study drug by gradual down-titration.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, neither the Investigator, study site personnel, subject, nor Sponsor (with the exception of the clinical supply colleagues responsible for the IVRS/IWRS and study drug management) should be unblinded to the treatment assignment of any subject for any reason except in the event of a medical emergency (eg, a life threatening event) or regulatory reporting requirement, if and when knowledge of the treatment assignment is considered necessary to determine the optimal medical management. Appropriate communications should take place between the study site and the Sponsor before accessing the IVRS/IWRS to allow unblinding of a subject's treatment assignment. In the event of a medical emergency that requires immediate unblinding, the IVRS/IWRS may be accessed by the Investigator to obtain treatment assignment information. In the event of a premature unblinding prior to Week 24, subjects will be discontinued from the study drug and should complete all remaining study visits.

Subjects who remain on study drug and complete the required study assessments through Week 24 will be eligible for an open-label study (Study TDE-HF-302). Following completion of the Week 24 assessments and entry of required data into the IVRS/IWRS, the

study site personnel will be unblinded to that subject's treatment assignment to determine the initial dose for the open-label study (Study TDE-HF-302). If the subject received oral treprostinil during the study, then the subject may remain on the same dose of study drug upon entry into the open-label study. If the subject received placebo during the study, then the subject should start treatment with oral treprostinil in the open-label study in accordance with that protocol.

Subjects who permanently discontinue study drug for any reason prior to Week 24 are not eligible for entry into the open-label study. The study site personnel will not be unblinded to the treatment assignment of these subjects unless required for safety reasons.

6.3 COMPLIANCE

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

Each subject will be provided with a dosing diary at each scheduled visit in order to record dosing information from randomization until Week 24. At scheduled study visits, subjects should be instructed to return all study drug (including empty and unused bottles) and their dosing diary to the study site. Upon return of study drug and the dosing diary at the Week 6, 12, 18, and 24 visits, the study coordinator or pharmacist must document the number of returned tablets of each strength on the subject's study drug accountability log 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. If it is determined that a subject is not compliant with study drug, then study 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, 18, and 24, and the Study Drug Termination Visit [if applicable]), all bottles of study drug will be

collected. Study drug returned at scheduled study visits will not be re-dispensed to the subject. Study site personnel will dispense a new supply of study drug at each protocol-required visit for the subsequent interval. If necessary, additional study drug may be dispensed in between protocol-required visits.

7 EXPERIMENTAL PROCEDURES

7.1 SCREENING PHASE

Study sites may conduct pre-Screening activities prior to a subject signing an ICF. Pre-Screening activities may include review of the study site's database to identify potential subjects that may be eligible for the study. The Screening phase will be conducted within 30 days prior to randomization and after informed consent has been obtained. The signing of informed consent will begin the 30-day window. The Screening and Baseline assessments may be conducted in 1 visit if all assessments are performed and all entry criteria are satisfied within the 48 hours prior to randomization and dosing with study drug.

The list of Screening assessments is displayed below:

- Informed consent
- Inclusion/exclusion criteria
- If necessary, the following procedures may be performed during the 30-day Screening phase if required to satisfy inclusion/exclusion criteria:
  - RHC
  - Pulmonary function tests
- ECHO

Medical records documenting eligibility criteria may also be used provided they document subject eligibility within the protocol-mandated timelines, as applicable. Results from the most recent RHC, including waveforms, and ECHO studies used in determining subject eligibility will be uploaded and stored in a central repository.

- Demographics
- PH history
- HF history
- Medical history

- Assessment of HF signs and symptoms (see Appendix 15.7) and vital signs (following at least 5 minutes of rest [seated])
- Physical examination
- Practice 6MWT/Borg dyspnea score (optional; serves as a practice test if the subject has not previously performed this test at the study site on the study-designated course; 6MWT is to be conducted following at least 10 minutes of rest [seated], and the Borg dyspnea score is to be conducted immediately following 6MWT)
- Clinical laboratory tests
- Urine pregnancy test for WOCBP
- Concomitant medications
- AE assessment
- Complete and submit Pre-Baseline Review Form

If a subject does not initially meet all entry criteria, they may be re-screened at a later date when any unusual or extenuating circumstances are adequately resolved. The Sponsor should be contacted prior to starting any re-screening assessments. Within the Screening Period, retests will be allowed if the results of any procedures or assessments are thought to be spurious, or if the underlying cause has been corrected. This would include, but is not limited to, laboratory-related entry criteria (eg, liver function parameters, renal function parameters, and hemoglobin values), the 6MWT, or pulmonary function tests.

7.2 BASELINE PHASE AND RANDOMIZATION

Baseline assessments can occur up to 48 hours prior to the first dose of study drug to allow for scheduling of all activities. The list of the Baseline Visit assessments is displayed below.

- Confirmation of remaining inclusion/exclusion criteria
- Assessment of HF signs and symptoms with vital signs (following at least 5 minutes of rest [seated])
- WHO Functional Class
- KCCQ
- Height and weight (body mass index)
- AE assessment
- Concomitant medications
- 12-lead ECG (following at least 5 minutes rest in the semi-recumbent position)
- ECHO (if not done previously during Screening)

- Clinical laboratory tests/NT-proBNP (NT-proBNP samples must be taken prior to the 6MWT and prior to the first dose of study drug)
- Collection of blood and urine samples for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of pharmacogenomics (optional)
- 6MWT/Borg dyspnea score (6MWT to be conducted prior to the first dose and following at least 10 minutes of rest [seated]; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment
- Urine pregnancy test for WOCBP (prior to randomization)
- Randomization via IVRS/IWRS (to be performed after all other Baseline assessments are completed and the Pre-Baseline Review Form has been approved by the Medical Monitor)
- First administration of study drug immediately (approximately 10 minutes) after consuming food
- Dosing instructions/dosing/accountability
- At least weekly telephone/email contact to begin following initiation of study drug up to Week 24 of treatment to monitor study drug compliance, AEs, signs and symptoms of disease, use of concomitant medications, occurrence of clinical worsening, and to make decisions regarding dose titration

7.3 TREATMENT PHASE

7.3.1 Weeks 6, 12, and 18 Assessments

The following assessments will be conducted at Weeks 6, 12, and 18 (the visit window is ±5 days from the projected visit date):

- Assessment for HF signs and symptoms with vital signs (following at least 5 minutes of rest [seated])
- WHO Functional Class
- AE assessment
- Dosing instructions/dosing/accountability
- Concomitant medications
- Clinical laboratory tests/NT-proBNP (Week 12 Visit only; NT-proBNP samples must be taken prior to the 6MWT)
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the most recent dose of study drug and following at least 10 minutes of rest [seated]; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment
- Urine pregnancy test for WOCBP

- Continue administration of study drug and dose titration
- Continue at least weekly telephone/email contact

7.3.2 Study Drug Termination Assessments

The assessments below will be conducted at the Study Drug Termination Visit. The Study Termination Visit is only applicable if a subject permanently discontinues study drug prior to Week 24. Subjects should not down-titrate their dose of study drug until after the Study Drug Termination Visit has been completed.

- Physical exam
- Assessment for HF signs and symptoms with vital signs (following at least 5 minutes of rest [seated])
- WHO Functional Class
- KCCQ
- AE assessment
- Dosing instructions/dosing/accountability
- 12-lead ECG (following at least 5 minutes rest in the semi-recumbent position)
- ECHO
- Concomitant medications
- Clinical laboratory tests/NT-proBNP (NT-proBNP samples must be taken prior to the 6MWT)
- Collection of blood and urine samples for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of pharmacogenomics (optional)
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the most recent dose of study drug and following at least 10 minutes of rest [seated]; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment (to continue for 7 days after the final dose of study drug if a subject permanently discontinues study drug during the Treatment Phase)
- Survival status (assessed 30 days [±5 days] after study drug discontinuation)
- Urine pregnancy test for WOCBP
- Telephone/email contact

7.3.3 Week 24 Assessments

The following assessments will be conducted at Week 24 (the visit window is ±5 days from the projected visit date; as needed, the completion of these assessments can occur over the visit window, but all assessments must be completed within window and prior to rollover into TDE-HF-302):

- Physical exam
- Assessment for HF signs and symptoms with vital signs (following at least 5 minutes of rest [seated])
- WHO Functional Class
- KCCQ
- AE assessment
- Drug accountability
- 12-lead ECG (following at least 5 minutes rest in the semi-recumbent position)
- ECHO
- Concomitant medications
- Clinical laboratory tests/NT-proBNP (NT-proBNP samples must be taken prior to the 6MWT)
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the most recent dose of study drug and following at least 10 minutes of rest [seated]; Borg dyspnea score to be conducted immediately following 6MWT)
- Clinical worsening assessment
- Survival status (assessed 30 days [±5 days] after study drug discontinuation)
- Urine pregnancy test for WOCBP
- Telephone/email contact
- Collection of blood and urine samples for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of pharmacogenomics (optional)

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or 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 significantly deviates 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 from the study prematurely, the Investigator must provide an explanation in the eCRF (eg, Investigator's Comment Log or other appropriate eCRF pages to provide an explanation of the reason) 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.

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 STUDY SITE

The study may also be terminated at a given center if any of the following occur:

- The Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the study site
- Violation of US Food and Drug Administration (FDA) regulations, International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, or national 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

All AEs/SAEs that occur while the subject is participating in the study will be recorded as instructed in this protocol (Section 9.2).

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered study drug, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of study drug, whether or not related to the use of the study drug. 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. The Investigator is responsible for recording all AEs that occur during the study beginning at Screening.

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.
- Worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (eg, exacerbation of a pre-existing illness following the start of the study or an increase in the frequency or intensity of a pre-existing episodic event or condition).

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

An AE does not include the following:

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

- Situations where an untoward medical occurrence has not occurred (eg, hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

Events attributable to the progression of the disease under study should only be recorded as an AE or SAE if the event is unusual with respect to intensity, frequency, duration as compared with symptoms in the subject's medical history, or if there is a reasonable possibility that the event was caused by the study drug (see Table 3-2).

9.1.2 Serious Adverse Event

An SAE is an AE which results in any of the following:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Results in a medically important event or reaction

Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent 1 of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse.

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE, such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome,

is also to be documented in the eCRF (see Appendix 15.3). 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 meaningful, or for at least 30 days if the AE extends beyond the final study 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 study 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 PREGNANCY

If a subject becomes pregnant during participation in this clinical study, study site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via email or fax to United Therapeutics Global Drug Safety (GDS; email:___; fax:__). 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. These subjects will be transitioned to an alternate therapy at the discretion of the Investigator. United Therapeutics GDS will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy. Pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to United Therapeutics GDS by email or fax (email: ___; fax: ___) within 24 hours of awareness. A completed SAE Notification Form, along with any relevant hospital records and autopsy reports should be sent to United Therapeutics GDS. A follow-up SAE Notification Form must be forwarded to

United Therapeutics GDS within 24 hours of the receipt of any new/updated information. The Investigator must also promptly notify their Institutional 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. Events attributable to the progression of the disease under study (see Table 3-2 and Section 3.3.2.3) are not to be reported to United Therapeutics as SAEs unless the event is unusual with respect to intensity, frequency, duration as compared with symptoms in the subject's medical history, or if there is a reasonable possibility that the event was caused by the study drug.

9.5 SAFETY REPORTS

In accordance with the US FDA, the Sponsor will notify the US 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. 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.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of all assessments will be transcribed into an eCRF by the appropriate study site personnel for each subject who signs an ICF until study completion or study discontinuation for any reason. A representative from the Sponsor will verify eCRF data fields against source documentation. All data transmitted from the study site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated and the database will be edited as appropriate. The eCRF data for each subject are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify their approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject's eCRF by the study site after the Investigator has applied his/her signature. The database will be considered final when all

outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

Approximately 310 subjects will be enrolled and randomly allocated to receive oral treprostinil or placebo. Using an allocation ratio of 1:1 between oral treprostinil and placebo, a sample size of 263 subjects would provide 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30-meter between-treatment difference in the change from Baseline to Week 24 in 6MWD, assuming a SD of 75 meters. The total sample size will be approximately 310 subjects to account for a discontinuation rate of approximately 15%. To ensure a final analysis population contains only subjects who were afforded the opportunity to reach their maximum tolerated dose, additional subjects may need to be enrolled up to an additional 15% overage, for a total maximum enrollment of 356 subjects.

10.3 ANALYSIS PLAN

Details of various efficacy and safety analyses are provided below. Further details will be documented in a statistical analysis plan prior to any unblinding of study data by the Sponsor. Additionally, a statistical analysis plan detailing the safety analyses for use at the DMC meetings will be generated to guide the independent statistical consultant tasked with performing these analyses. All statistical calculations will be done using SAS version 9.4 or above (SAS Institute Inc., Cary, NC, USA).

The Intent-to-Treat (ITT) Population will be defined as all subjects randomized into the study that receive at least 1 dose of study drug; all subjects will be counted in the group to which they were randomized, regardless of the treatment they were actually given. All efficacy analyses will be performed on this ITT Population. Additional efficacy analyses may be performed on further populations to be defined in the detailed statistical analysis plan.

10.3.1 Primary Efficacy Endpoint

The primary hypothesis is that oral treprostinil will increase the distance traversed in the 6MWT at Week 24 over placebo in subjects with PH associated with HFpEF. The effect of oral treprostinil versus placebo on change from Baseline to Week 24 in 6MWD will be

analyzed using an analysis of covariance (ANCOVA) with Baseline 6MWD as the covariate (if the assumptions for ANCOVA do not hold, the nonparametric analysis of variance [ANOVA] may be used). For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 24; the exception being subjects who die. For subjects who die prior to Week 24, a 6MWD of 0 meters will be imputed at Week 24. For subjects who discontinue study drug prior to Week 24, but remain in the study for the duration of the treatment period, their last on-drug 6MWD will be carried forward to Week 24 for analysis. The worst case imputation and other imputation techniques will be employed to investigate the impact of the missing data.

10.3.2 Secondary Efficacy Endpoints

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

1. Change in NT-proBNP levels from Baseline to Week 24
2. Time to the first clinical worsening event
3. Change in WHO Functional Class from Baseline to Week 24

In order to control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed-sequence) testing procedure. The change in NT-proBNP levels from Baseline to Week 24 will be tested at a 2-sided Type 1 error rate of 0.05. The subsequent tests for other secondary efficacy endpoints will be tested only if the preceding test is statistically significant.

10.3.3 Exploratory Efficacy Endpoints

The following exploratory endpoints will be summarized and analyzed to assess the treatment effect without adjustment for multiplicity:

1. Change in 6MWD from Baseline to Weeks 6, 12, and 18
2. Change in Borg dyspnea score from Baseline to Weeks 6, 12, 18, and 24
3. Change in NT-proBNP levels from Baseline to Week 12
4. Change in WHO Functional Class from Baseline to Weeks 6, 12, and 18
5. Change in HbA1c from Baseline to Week 24
6. Change in KCCQ from Baseline to Week 24

10.3.4 Efficacy Analyses

10.3.4.1 Time to Clinical Worsening

Clinical worsening is defined in Section 2.2. The time from the first dose of study drug until to the first clinical worsening event will be summarized using Kaplan-Meier estimates, and compared between treatment groups using the log-rank test. The incidence of clinical worsening events will be summarized and compared between treatment groups using Fisher's exact test.

10.3.4.2 N-Terminal Pro-brain Natriuretic Peptide

Changes from Baseline to each follow-up assessment in plasma NT-proBNP will be summarized and analyzed using an ANCOVA, using baseline NT-proBNP values as the covariate.

10.3.4.3 WHO Functional Class

Changes from Baseline to each follow-up assessment in WHO Functional Class will be summarized and compared between treatment groups using the Wilcoxon rank-sum test. The number and percentage of subjects with WHO Functional Class improvement, no change, and worsening will be summarized by treatment group.

10.3.4.4 6-Minute Walk Distance

The effect of oral treprostinil versus placebo on change from Baseline to Week 24 in 6MWD will be analyzed as described above for the primary endpoint. Descriptive statistics will be used to summarize the 6MWD data at Baseline and Weeks 6, 12, and 18.

10.3.4.5 Borg Dyspnea Score

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

10.3.4.6 Kansas City Cardiomyopathy Questionnaire

Responses to the KCCQ will be summarized utilizing the published scoring algorithms to provide an overall summary score and individual scores within the following specific health domains pertaining to heart failure: physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life. Values for

each domain range from 0 to 100; higher scores indicate lower symptom burden and better quality of life. Changes from Baseline to Week 24 in domain and overall scores for the KCCQ will be summarized and compared between treatment groups using an ANCOVA method.

10.3.5 Safety Analyses

The Safety Population will be defined as all subjects in the study that receive study drug (regardless of randomization status), and all subjects will be counted in the group corresponding to the treatment that they actually received. If a subject received oral treprostinil at any point during the study, he/she will be counted in the oral treprostinil treatment group within the Safety Population. All safety analyses will be performed on the Safety Population.

The safety of oral treprostinil will be evaluated through comparisons of AEs, assessment of heart failure signs and symptoms with vital signs, clinical laboratory parameters, ECGs, and ECHOs between treatment groups. All AEs as recorded by the Investigators will be assigned Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms by the Sponsor for reporting purposes. For all safety endpoints, tabular summaries will be provided.

10.4 INTERIM ANALYSIS

No formal interim analysis for efficacy data will be performed. Analyses of safety data for review by the independent DMC will be performed after approximately 10, 30, 60, 100, and 200 subjects have been enrolled in the study, or on an ad hoc basis per request of the independent DMC, as necessary. Enrollment will not be stopped during the DMC reviews; however, subjects may not progress to the next highest maximum dose level until the DMC provides their review of the data. All interim analyses will be performed by a statistical consultant independent and external to the Sponsor. This statistical consultant will have access to the unblinded study data and will prepare the necessary output for review by the DMC as defined in the DMC charter. The Sponsor will only have access to blinded study data during these interim analyses.

10.5 OTHER ANALYSES

Other exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the final clinical study report. In general, listings will be sorted by subject and scheduled assessment (if applicable). For summary tables, in general, the data will be summarized by scheduled assessment. For continuous variables, descriptive statistics will include the number of observations, mean, SD, median, minimum, and maximum. For categorical variables, descriptive statistics will include the frequency and percent in each category.

10.7 DATA MONITORING COMMITTEE

An independent DMC will be established for the study, composed of a minimum of 3 independent members, 1 physician knowledgeable in the treatment of PH, 1 physician knowledgeable in the treatment of HF, and 1 statistician. Throughout the course of the study, the DMC will meet on a regular basis to monitor the safety of the study and make changes to maximum dosages of study drug to be used in accordance with the DMC Charter. The frequency of meetings will depend on the rate of enrollment and the rate of occurrence of SAEs, as outlined in the DMC Charter. The DMC will be masked to individual subject treatment allocation during the review process. Analyses of safety data will be performed after approximately 10, 30, 60, 100, and 200 subjects have been enrolled in the study, or on an ad hoc basis per request of the independent DMC, as necessary. Enrollment will not be stopped during the DMC reviews; however, subjects may not progress to the next highest maximum dose level until the DMC provides their review of the data. The analyses will be prepared by an independent external statistical consultant and reviewed only by the DMC as defined in the DMC Charter. The Sponsor will only have access to blinded study data during this process.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

United Therapeutics Corporation will supply study drug (oral treprostinil and placebo) for administration during the study. The oral treprostinil tablets are SR osmotic tablets. Active

treatment will be oral treprostinil tablets provided as 0.125-, 0.25-, 1-, and 2.5-mg strengths for the study. Each tablet contains either 0.125 mg treprostinil (equivalent to 0.159 mg treprostinil diethanolamine), 0.25 mg treprostinil (equivalent to 0.317 mg treprostinil diethanolamine), 1 mg treprostinil (equivalent to 1.27 mg treprostinil diethanolamine), 2.5 mg treprostinil (equivalent to 3.17 mg treprostinil diethanolamine), or no treprostinil (placebo). The 0.125-, 0.25-, 1-, and 2.5-mg tablets are colored blue, green, yellow, and pink, respectively. Oral treprostinil tablets and matching placebo tablets will be provided in child resistant bottles, each containing 100 tablets.

11.2 LABELING

Each bottle and/or kit will be labeled in accordance with applicable national regulations, to include at least the following information: study drug, 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 study 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 STUDY MATERIAL

All study drug will be stored at room temperature (25°C [77°F]) with excursions permitted to 15°C to 30°C (59°F to 86°F). Study drug should not be frozen, refrigerated, or exposed to heat. Study site personnel should refer to study drug labeling or regulatory submissions for specific requirements by country or region in accordance with local regulations or guidance.

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

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At randomization, an IVRS/IWRS will be utilized by study site personnel to randomize each subject and assign the appropriate study drug bottles for the first 6-week treatment interval. At subsequent visits to the study site, the IVRS/IWRS will be utilized by study site personnel to assign new study drug bottles to each subject based upon their current dose of study drug and the length of time until the next protocol-required visit. Additional study drug supply may occur between protocol-required visits as required. At each protocol-required study visit, all unused study drug dispensed to the subject should be returned to the study site (including empty and unopened bottles).

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records will be maintained during the study, and these records will include the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of unused drug returned or destroyed. At each visit, study 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 can be returned to a Sponsor-designated location for destruction.

Study drug may be destroyed on site provided the institution has written policies and/or procedures in place describing their process and maintains all documentation related to on-site destruction. Prior to proceeding with on-site destruction, the site should notify the Sponsor for review of their policies and/or procedures. For sites that perform on-site destruction of study drug, accountability by the Sponsor may not be performed prior to destruction.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 US FDA OR APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with the ICH GCP guidelines and all applicable national regulations. The study will be conducted in Canada, Mexico, and the US. 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 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 study site, the Investigator will obtain approval for the study from an appropriate IRB/EC and provide the Sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's ICF and any other written information provided to the subject 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 standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

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

The study 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, Financial Disclosure Form, IRB/EC Composition and Roster, IRB/EC protocol and ICF approval letters, and Curriculum Vitae of study staff listed on the Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

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

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

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

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

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

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify 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 study 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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15 APPENDICES

15.1 PROCEDURES FOR 6-MINUTE WALK TEST AND BORG DYSPNEA SCALE

General Procedures

The 6MWT should be administered by the same tester at each study site throughout the study. 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 study site. If the subject was assessed at Baseline using oxygen therapy, then all 6MWTs during the study should be conducted with the same oxygen flow rate and mode of administration. Similarly, if the Baseline assessment was conducted without oxygen therapy, then subsequent assessments should also be conducted without oxygen therapy. Before each 6MWT, the subject should rest (seated) for at least 10 minutes.

The area used for the 6MWT should be premeasured at approximately 30 meters in length (but no shorter than 15 meters [16 yards or 50 feet] in length) and approximately 2 to 3 meters in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well-ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested, but the clock will continue to run. At the end of 6 minutes, the tester will call "stop where you are" while simultaneously stopping the watch, and then measure the distance walked.

Instructions to the Subject

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

> "The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may

stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

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

"Do you have any questions about the test?"

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

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

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

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

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

"Stop where you are."

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

Borg Dyspnea Score

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

"I would like to use the following scale to describe how out of breath you are (indicate the scale). This scale uses 0 for no shortness of breath at all and 10 is the worst shortness of breath you have ever had. Please point to a number that tells me how short of breath you feel right now."

15.2 WHO FUNCTIONAL CLASSIFICATION FOR PULMONARY HYPERTENSION

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

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

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

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

15.3 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

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

"How are you doing (feeling)?"

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

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

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

Using provided definitions, the Investigator will then:

(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

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

INTENSITY

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

SERIOUSNESS

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

*Hospitalizations that would not be considered SAEs include those for:

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

CAUSALITY

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

Definitions of the causality categories are as follows:

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

- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:
- Has a reasonable temporal relationship to study drug
- The event has a plausible biological link to the activity of the study drug
- Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration, or complication
- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge—the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
- Has a reasonable temporal relationship to study drug
- The event has a plausible biologic link to the activity of the study drug
- Not readily explained by an intercurrent illness
- Not readily explained by external event
- Improves on discontinuation of study drug
- If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION

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

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

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.
- Recovered/Resolved with Sequelae – The AE is considered resolved; however, there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.
- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the AE cannot be determined.

15.4 CLINICAL LABORATORY PARAMETERS

Blood Chemistries	Hematology	Other
Sodium	Red blood cell count	N-terminal pro-brain natriuretic peptide (NT-proBNP)
Potassium	Hemoglobin	Urine pregnancy test[a]
Chloride	Hematocrit	
Bicarbonate/CO_2	Platelet count	
Albumin	White blood cell count	
Blood urea nitrogen/urea	Glycated hemoglobin (HbA1c)	
Total bilirubin		
Indirect bilirubin		
Direct bilirubin		
Alkaline phosphatase		
Alanine aminotransferase (ALT)		
Aspartate aminotransferase (AST)		
Gamma-glutamyl transferase (GGT)		
Creatinine		

[a] Urine pregnancy test for women of childbearing potential

Visit Test Schedule

Visit	Labs Collected
Screen[b]	Chemistries, Hematology, urine pregnancy[a]
Baseline[b]	Chemistries, Hematology, NT-proBNP, urine pregnancy[a]
Week 6	Urine pregnancy[a]
Week 12	Chemistries, Hematology, NT-proBNP, urine pregnancy[a]
Week 18	Urine pregnancy[a]
Study Drug Termination	Chemistries, Hematology, NT-proBNP, urine pregnancy[a]
Week 24	Chemistries, Hematology, NT-proBNP, urine pregnancy[a]

NT-proBNP, N-terminal pro-brain natriuretic peptide
[a] Urine pregnancy tests for women of childbearing potential only
[b] If combining Screening and Baseline visits, utilize Baseline laboratory kit type

15.5 CHILD-PUGH SCORE

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

Class A (mild) = 5 to 6 points

Class B (moderate) = 7 to 9 points

Class C (severe) = 10 to 15 points

15.6 KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

15.7 EVALUATION OF SIGNS/SYMPTOMS OF HEART FAILURE AND VITAL SIGNS

Vital signs should be collected prior to the 6MWT (following at least 5 minutes of rest [seated]; no other measurements or procedures should be performed during this 5-minute period). If vital signs cannot be obtained prior to the 6MWT, then they should be obtained after a minimum 30-minute recovery from the 6MWT. The following vital signs and heart failure signs and symptoms should be evaluated at each study visit.

Vital Signs

1. Blood pressure-peripheral (radial/brachial artery)
2. Heart rate
3. Respiratory rate
4. Weight
5. Height (collected at the Baseline Visit only)

Heart Failure Signs and Symptoms

1. Peripheral edema (none, trace, 1+, 2+, 3+)
2. Jugular venous pressure (present, absent)
3. Breath sounds: clear, diminished, rhonchi, wheezes, rales (present/absent)
4. Ascites (present/absent)
5. Dyspnea (at rest, minimal activity, exertional activity, none, or with vigorous activity only)
6. Orthopnea (present/absent)
7. Paroxysmal nocturnal dyspnea (present/absent)
8. Decreased appetite/bloating/early satiety compared with Baseline (present/absent)
9. Syncope (present/absent)
10. Chest pain (present/absent)
11. Fatigue (none, mild, moderate, severe)