An Open-label Extension Study of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF) - A Long-term Follow-up to Study TDE-HF-301

IND Number 133,962

Protocol TDE-HF-302

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	28 December 2016
Amendment 1	19 September 2017
Amendment 2	11 February 2019

LIST OF CONTACTS FOR STUDY

Contract Research Organization	
Study Sponsor	
Central Clinical Laboratory	3

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "An Open-label Extension Study of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF) - A Long-term Follow-up to Study TDE-HF-301" Amendment 2, dated 11 February 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 (EC)/Institutional Review Board (IRB) approval documents have been obtained.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	An Open-label Extension Study of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF) – A Long-Term Follow-up to Study TDE-HF-301
Study Phase	3
Indication	Pulmonary hypertension associated with HFpEF
Primary Objective	The primary objective of this study is to evaluate the long-term safety of oral treprostinil in subjects with PH associated with HFpEF for subjects who completed Study TDE-HF-301.
Secondary Objective(s)	To assess the effect of continued long-term therapy with oral treprostinil on the following: • 6-Minute Walk Distance (6MWD) • Borg dyspnea score • World Health Organization (WHO) Functional Class • N-Terminal pro-brain natriuretic peptide (NT-proBNP) at Weeks 24 and 48
Study Design	Multi-center, open-label study for eligible patients who completed Study TDE-HF-301
Sample Size	Approximately 310 subjects from Study TDE-HF-301 will be enrolled
Summary of Subject Eligibility Criteria	Participation and completion of required visits from Study TDE-HF-301
Drug Dosage and Formulation	All subjects will receive oral treprostinil sustained release tablets. Study drug will be provided in 0.125-, 0.25-, 1-, and 2.5-mg sustained release tablets. For subjects who were randomly allocated to oral treprostinil in Study TDE-HF-301, the initial dose of oral treprostinil will be based upon the final dose in Study TDE-HF-301. For subjects who were randomly allocated to placebo in Study TDE-HF-301, the initial dose of oral treprostinil will be initiated at 0.125 mg 3 times daily (TID).
Control Group	None
Route of Administration	Oral

Procedures	Study visits will occur at Baseline, Weeks 6, 12, 18, 24, and every 12 weeks thereafter. Study visits will continue until either the subject discontinues the study or until the study is discontinued by the Sponsor. Study assessments include: • 6-Minute Walk Test (6MWT)/Borg dyspnea score • WHO Functional Class • NT-proBNP (Weeks 24 and 48 only) • Safety (assessment of heart failure signs and symptoms with vital signs, adverse events (AEs), clinical laboratory assessments, concomitant medications
Statistical Considerations	All data will be summarized in tables and listings.
Sponsor	United Therapeutics Corp. 55 TW Alexander Dr. P.O. Box 14186 Research Triangle Park, NC 27709 USA

TABLE OF CONTENTS

LIST OF CONTACTS FOR STUDY 2
INVESTIGATOR'S AGREEMENT 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 6
Table of In-Text Tables 8
LIST OF ABBREVIATIONS 9
1 BACKGROUND AND RATIONALE 11
1.1 DEFINITION OF CLINICAL PROBLEM 11
1.2 TREPROSTINIL DIETHANOLAMINE BACKGROUND 12
1.2.1 General Pharmacology 12
1.2.2 General Toxicology 13
1.2.3 Clinical Pharmacology 14
1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION 16
1.4 CLINICAL HYPOTHESIS 19
2 OBJECTIVES 19
2.1 PRIMARY OBJECTIVE 19
2.2 SECONDARY OBJECTIVES 19
2.3 SAFETY ENDPOINTS 20
3 EXPERIMENTAL PLAN 20
3.1 STUDY DESIGN 20
3.2 SCHEDULE OF TIMES AND EVENTS 21
3.3 CLINICAL ASSESSMENTS 23
3.3.1 Efficacy 23
3.3.1.1 6-Minute Walk Test 23
3.3.1.2 Borg Dyspnea Score 23
3.3.1.3 WHO Functional Class 23
3.3.1.4 NT-proBNP 23
3.3.2 Safety 23
3.3.2.1 Assessment of Heart Failure Signs and Symptoms with Vital Signs 23
3.3.2.2 Physical Examination 24
3.3.2.3 Clinical Laboratory Assessments 24
3.3.2.4 Adverse Event Assessments 24
3.3.2.5 Pregnancy Testing 25
3.3.2.6 Concomitant Medications 25
3.4 NUMBER OF CENTERS 26
3.5 NUMBER OF SUBJECTS 26
3.6 ESTIMATED STUDY DURATION 26

4 SUBJECT ELIGIBILITY 26
4.1 INCLUSION CRITERIA 26
4.2 EXCLUSION CRITERIA 27
4.3 PRESCRIBED THERAPY 27
4.3.1 Concomitant Medications 27
5 SUBJECT ENROLLMENT 27
5.1 TREATMENT ASSIGNMENT 27
5.2 RANDOMIZATION 27
5.3 BLINDING 27
6 DRUGS AND DOSING (OR TREATMENT PROCEDURES) 27
6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE 27
6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT 30
6.3 COMPLIANCE 30
7 EXPERIMENTAL PROCEDURES 31
7.1 TREATMENT PHASE 31
7.1.1 Baseline 31
7.1.2 Week 6 Visit 32
7.1.3 Week 12 Visit 33
7.1.4 Week 18 Visit 33
7.1.5 Week 24 Visit 33
7.1.6 Follow-up Visits (Every 12 Weeks) 33
7.1.7 Study Termination Visit 34
8 STUDY TERMINATION 35
8.1 CRITERIA FOR SUBJECT WITHDRAWAL 35
8.2 CRITERIA FOR TERMINATING THE STUDY 35
8.3 CRITERIA FOR DISCONTINUING THE STUDY SITE 35
9 ADVERSE EVENT REPORTING 36
9.1 DEFINITIONS 36
9.1.1 Adverse Event 36
9.1.2 Serious Adverse Event 37
9.2 DOCUMENTATION OF ADVERSE EVENTS 37
9.3 PREGNANCY 38
9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR 38
9.5 SAFETY REPORTS 39
10 STATISTICAL CONSIDERATIONS 39
10.1 DATA PROCESSING 39
10.2 SAMPLE SIZE 40
10.3 ANALYSIS PLAN 40
10.4 OTHER ANALYSES 40
11 PACKAGING AND FORMULATION 40

11.1 CONTENTS OF STUDY DRUG 40
11.2 LABELING 40
11.3 STORAGE AND HANDLING OF CLINICAL STUDY MATERIAL 41
11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL 41
11.5 DRUG ACCOUNTABILITY 41
12 REGULATORY AND ETHICAL OBLIGATION 42
12.1 ICH GCP OR APPLICABLE REGULATORY REQUIREMENTS 42
12.2 INFORMED CONSENT REQUIREMENTS 42
12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD 42
12.4 PRESTUDY DOCUMENTATION REQUIREMENTS 43
12.5 SUBJECT CONFIDENTIALITY 43
13 ADMINISTRATIVE AND LEGAL OBLIGATIONS 44
13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION 44
13.2 STUDY DOCUMENTATION AND STORAGE 44
13.3 STUDY MONITORING AND DATA COLLECTION 44
14 REFERENCES 46
15 APPENDICES 49
15.1 PROCEDURE FOR 6-MINUTE WALK TEST AND BORG DYSPNEA SCORE 49
15.2 WHO FUNCTIONAL CLASSIFICATION FOR PULMONARY HYPERTENSION 51
15.3 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS 52
15.4 CLINICAL LABORATORY PARAMETERS 56
15.5 EVALUATION OF SIGNS/SYMPTOMS OF HEART FAILURE AND VITAL SIGNS 57

Table of In-Text Tables

Table 3-1 Overall Schedule of Time and Events 21
Table 3-2 Expected Events Attributable to the Progression of the Disease Under Study 25
Table 7-1 Follow-up Visits by Week Beyond Week 24 34

LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
AUC	Area under the curve
BID	Twice daily
C_{max}	Maximal drug concentration
CYP	Cytochrome P450
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
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
IV	Intravenous(ly)
IVRS/IWRS	Interactive voice or web response system
LV	Left ventricular
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
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
RV	Right ventricle
SAE	Serious adverse event
SC	Subcutaneous

SD	Standard deviation
TID	3 times daily
US	United States
UT	United Therapeutics
UT-15C SR	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 (Simonneau 2013). This classification includes PH due to left ventricular systolic and diastolic dysfunction, valvular heart disease, inflow/outflow tract obstruction, and congenital cardiomyopathies. 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 'post-capillary' 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 'pre-capillary' 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 post-capillary PH (Hussain 2016).

Heart failure affects 1% to 2% of the adult population in developed countries, and HFpEF represents up to 70% 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 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 a sustained-release 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 patients 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 administered oral treprostinil 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 increase 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 Practice (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 (BID; 4 mg/kg/day) to male beagle dogs was not associated with any definitive changes in arterial pressure, heart rate, or electrocardiogram parameters. In addition, no abnormal clinical signs were noted in the animals dosed with the vehicle or with any of the doses of diethanolamine.

1.2.3 Clinical Pharmacology

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 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 curve [AUC]) indicate that Day 1 PK data are predictive of Day 13 and linearity was observed in plasma exposure comparing 1- 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. On Day 7, the mean maximal drug concentration (C_{max}; ± standard deviation [SD]) was 0.810±0.491 ng/mL, occurring at a median time of 14 hours (range: 6 to 20 hours) following the morning dose. This indicates that maximum concentration during a daily interval at steady state occurs after the evening (or third) dose of the day.

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

On Day 7, the mean C_{max} (±SD) was 0.810±0.491 ng/mL, occurring at a median time of 14 hours (range: 6 to 20 hours) following the morning dose. This indicates 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.

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

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

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Oral treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in subjects with WHO Group I 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 transmission of backward pressures caused by LV diastolic dysfunction (Guazzi 2011). Another study followed 244 HFpEF subjects over 3 years to assess the disease severity in subjects with PH associated with HFpEF versus subjects with hypertension 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 is 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 subjects with PH associated with HFpEF (LVEF>50%) 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=0.004) 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, 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 (ERA), 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 is 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 (Redfield 2013, 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 HFpEF associated with PH, 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 open-label study will evaluate the safety of continued therapy with oral treprostinil in subjects who have completed Study TDE-HF-301. This study will provide long-term, open-label data regarding the safety and efficacy of oral treprostinil for the treatment of PH associated with HFpEF.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the long-term safety of oral treprostinil in subjects with PH associated with HFpEF for subjects who completed Study TDE-HF-301.

2.2 SECONDARY OBJECTIVES

Secondary objectives of this study are:

- To assess the effect of continued long-term therapy with oral treprostinil on the following:
  - 6MWD
  - Borg dyspnea score
  - WHO Functional Class
  - N-Terminal pro-brain natriuretic peptide (NT-proBNP) at Weeks 24 and 48

2.3 SAFETY ENDPOINTS

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

- AEs
- Clinical laboratory parameters
- Physical assessment of heart failure signs and symptoms with vital signs

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is an open-label study. Subject visits will occur at Baseline, Weeks 6, 12, 18, 24, and every 12 weeks thereafter (see Table 3-1). The study will continue until either oral treprostinil becomes commercially available to treat PH associated with HFpEF or the study is discontinued by the Sponsor.

3.2 SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Time and Events

Study Procedures		Treatment Phase					
Study Week	**Baseline[a] (Study Entry)**	**Week 6[b]**	**Week 12[b]**	**Week 18[b]**	**Week 24[b]**	**Follow-up Visits (Every 12 Weeks[b])**	**Study Termination**
Study day	1	43	85	127	169		
Informed consent	X						
Subject eligibility (inclusion/exclusion criteria)	X						
Physical examination	X						X
Assessment of heart failure signs and symptoms with vital signs[c]	X	X	X	X	X	X	X
WHO Functional Class	X	X	X	X	X	X	X
Clinical laboratory assessments	X		X		X	X[d]	X
NT-proBNP[e]	X				X	X	
Urine pregnancy test[f]	X	X	X	X	X	X	X
6MWT/Borg dyspnea score[g]	X	X	X	X	X	X	X
Dosing instructions/ dosing/accountability[h]	X--	--X--	--X--	--X--	--X--	--X--	--X
Weekly/monthly telephone/email contact[i]	X--	--X--	--X--	--X--	--X--	--X--	--X
Adverse events[j]	X--	--X--	--X--	--X--	--X--	--X--	--X
Concomitant medications	X--	--X--	--X--	--X--	--X--	--X--	--X

Abbreviations: 6MWT, 6-Minute Walk Test; AE, adverse event; NT-proBNP, N-terminal pro-brain natriuretic peptide; TID, 3 times daily; WHO, World Health Organization

[a] Baseline assessments for this study are those collected at the Week 24 visit from Study TDE-HF-301 and prior to initiation of open-label study drug. The exceptions to this are the Informed Consent Form and inclusion/exclusion criteria specific to this protocol.

[b] The visit window is ±7 days through Week 24 and ±14 days starting with the follow-up visits.

[c] Refer to Appendix 15.5 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.

[d] During the follow-up visits, clinical laboratory samples should be collected every 24 weeks.

[e] Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT and will occur prior to the first dose of TDE-HF-302 study drug at Baseline (done as part of TDE-HF-301 Week 24 assessments). NT-proBNP will be collected at Baseline, Week 24, and Week 48 (Follow-up Visit 2) only.

[f] For females of childbearing potential only.

[g] All 6MWTs 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 by simple face mask at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[h] Once all entry criteria have been met, the first dose of study drug will be administered at the study site with food. The initial dose of study drug will be dependent on the treatment assignment from Study TDE-HF-301. Those subjects who were assigned to placebo will begin dosing at 0.125 mg TID and those subjects who were assigned to active will remain on the previous dose of study drug. Study drug dosing will continue TID (every 6 to 8 hours).

[i] At least weekly telephone/email contact is required through the first 24 weeks of the study and monthly thereafter (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). 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 meaningful AEs or other emergent issues.

[j] All AEs ongoing at the Week 24 visit from Study TDE-HF-301 will be recorded as continuing AEs in this open-label study. The AEs will be documented from the time of informed consent until the subject is discontinued from the study 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.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 6-Minute Walk Test

A 6-Minute Walk Test (6MWT; described in Appendix 15.1) will be conducted at Baseline as part of study termination assessments from Study TDE-HF-301, and at Weeks 6, 12, 18, 24, every 12 weeks thereafter, and at the study termination visit. Before each 6MWT, the subject should rest (seated) for at least 10 minutes. The 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area that meets the requirements outlined in Appendix 15.1 (ATS 2002, Holland 2014). The 6MWT should be conducted 3 to 6 hours after the most recent dose of oral treprostinil. This 3- to 6-hour time window does not apply to subjects who are currently on a prescribed zero dose.

3.3.1.2 Borg Dyspnea Score

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

3.3.1.3 WHO Functional Class

The subject's WHO Functional Class for PH (Appendix 15.2) will be assessed at Baseline as part of study termination assessments from Study TDE-HF-301, and at Weeks 6, 12, 18, 24, every 12 weeks thereafter, and at the study termination visit.

3.3.1.4 NT-proBNP

The NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). The NT-proBNP sample collection will occur at Baseline as part of study termination assessments from Study TDE-HF-301, Week 24, and Week 48 (Follow-up Visit 2).

3.3.2 Safety

3.3.2.1 Assessment of Heart Failure Signs and Symptoms with Vital Signs

Symptoms of heart failure (Appendix 15.5) will be assessed at Baseline as part of the study termination assessments from Study TDE-HF-301, and at Weeks 6, 12, 18, 24, every

12 weeks thereafter, and at the study termination visit. 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. All vital signs will be collected prior to or at least 30 minutes following the corresponding 6MWT to ensure accurate measurement. Vital signs include blood pressure, height, weight, peripheral (radial/brachial artery) heart rate, and respiration rate.

3.3.2.2 Physical Examination

A physical examination will be assessed at Baseline as part of study termination assessments from Study TDE-HF-301 and at the study termination visit.

3.3.2.3 Clinical Laboratory Assessments

Clinical laboratory parameters will be assessed at Baseline as part of study termination assessments from Study TDE-HF-301. Clinical laboratory assessments will also be assessed at Weeks 12 and 24, at every 24 weeks thereafter, and at the study termination visit. Clinical laboratory parameters to be assessed at the study visits are listed in Appendix 15.4. A urine pregnancy test will be collected for women of childbearing potential (WOCBP) at each study visit.

3.3.2.4 Adverse Event Assessments

Any AEs that are ongoing at the study termination visit from Study TDE-HF-301 should be recorded as continuing AEs in this open-label study.

AEs will be captured from the time the Informed Consent Form (ICF) is signed. All AEs should be followed until resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically meaningful, or for up to 30 days if the AE extends beyond the final visit. All serious adverse events (SAEs) should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 30 days after completion of the final visit. Sections 9.1.1 and 9.1.2 and Appendix 15.3 provide the guidelines and definitions for recording AEs.

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 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.

3.3.2.5 Pregnancy Testing

All WOCBP will undergo a urine pregnancy test at Baseline as part of study termination assessments from Study TDE-HF-301 and at Weeks 6, 12, 18, 24, every 12 weeks thereafter, and at the study termination visit. 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.

3.3.2.6 Concomitant Medications

Concomitant medication may be adjusted as deemed clinically necessary by the Investigator during the study. However, additional prostanoid therapies should not be added. Concomitant medications used during the study will be reviewed at each protocol-required visit and recorded as they are prescribed in the electronic Case Report Form (eCRF). Concomitant medications that were ongoing at the end of Study TDE-HF-301 will be recorded in the eCRF for the open-label study.

3.4 NUMBER OF CENTERS

The study sites who participate in Study TDE-HF-301 (approximately 100) will take part in the study.

3.5 NUMBER OF SUBJECTS

Approximately 310 subjects from Study TDE-HF-301 may be eligible to participate in the study.

3.6 ESTIMATED STUDY DURATION

It is estimated that the study will continue for 4 years; however, this could last longer. The study may be discontinued at any time if, in the opinion of the Investigators and/or Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time. Subjects that discontinue the study will be contacted approximately 30 days (±5 days) after study drug discontinuation to confirm their survival status. Subjects may also continue to be contacted after the final study visit to assess AEs/SAEs (see Section 9.2 for additional details).

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

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

1. The subject voluntarily provides informed consent to participate in the study.
2. The subject participated in Study TDE-HF-301, remained on study drug, was compliant with study procedures and assessments during Study TDE-HF-301, and completed through Week 24 of that study.
3. All WOCBP must have a negative urine pregnancy test at Baseline (completed as part of Week 24 assessments from Study TDE-HF-301) prior to initiating Study TDE-HF-302 study drug.

   The WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months). The WOCBP must practice true abstinence from intercourse when it is in line with their preferred and usual lifestyle, or use 2 different forms of highly effective contraception for the duration of the study, and for at least 30 days

after discontinuing study medication. Medically acceptable forms of effective contraception include: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device, or (4) partner vasectomy. Male subjects with a partner of child-bearing potential, must use a condom during the length of the study, and for at least 48 hours after discontinuing study medication.

4.2 EXCLUSION CRITERIA

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

1. The subject is pregnant or lactating.
2. The subject was prematurely discontinued from Study TDE-HF-301 for any reason.
3. The subject developed a concurrent illness or condition during the conduct of Study TDE-HF-301, which, in the opinion of the Investigator, would represent a risk to the subject's overall health if they enrolled in this study.

4.3 PRESCRIBED THERAPY

4.3.1 Concomitant Medications

In this open-label study, there are no restrictions on concomitant medications with the exception that other prostanoid therapy should not be added.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

All subjects will receive oral treprostinil sustained release tablets during this open-label study. Subjects will retain the same subject number as assigned for the TDE-HF-301 study.

5.2 RANDOMIZATION

This study is not randomized.

5.3 BLINDING

This study is not blinded.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

The oral treprostinil tablets are sustained-release 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.

For subjects who were randomly allocated to receive placebo in Study TDE-HF-301, dosing of oral treprostinil will be initiated and optimized as described in the Study TDE-HF-301 protocol, including all safety monitoring and periodic telephone/email contacts. That is, the first dose of oral treprostinil (0.125 mg) should be taken by the subject at the study site immediately after (~10 minutes) consuming food. Oral dosing of study drug will be continued at 0.125 mg TID (every 6 to 8 hours) immediately after (~10 minutes) consuming food. Subjects must be instructed to take the appropriate amount of oral treprostinil 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 maximal difference during each titration between the lowest dose and the highest dose cannot exceed 0.125 mg. The maximum allowed dose will be identical to TDE-HF-301. The anticipated maximum allowed dose during the study will be 6 mg TID. The Data Monitoring Committee (DMC) will meet at predetermined intervals during Study TDE-HF-301. Any decision impacting the maximum dose will be relayed to all study sites following the DMC meetings.

Subjects who were randomly allocated to receive oral treprostinil in Study TDE-HF-301 will begin the open-label study at the same dose they were receiving at the Week 24 visit in Study TDE-HF-301, and subsequent adjustments will be made based on symptoms of PH and adverse effects while continuing to observe the maximum study drug dose permitted by the DMC.

All subjects must be instructed to take the appropriate amount of 0.125-, 0.25-, 1-, and/or 2.5-mg tablets based upon their prescribed dose. All dose changes should be conducted under appropriate medical supervision in consultation with the study site. Weekly telephone calls/emails between study site personnel and the subject should be made during the first

24 weeks of the study to monitor AEs and make decisions about dose titration. After Week 24, monthly telephone calls/emails should be made to continue to monitor AEs and make decisions regarding appropriate dose titrations. If dose titration is considered appropriate, study site personnel will instruct the subject to modify their dose and the dose change will be recorded in source documentation. If it becomes necessary for a subject to modify their dose of oral treprostinil (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 oral treprostinil. If dosing is interrupted for longer than 24 hours, consideration should be given to gradually re-titrating the subject's dose to the last dose administered prior to the dose interruption. In the event of a planned, short-term interruption of study drug for subjects unable to take oral medications during the study, study sites should contact the United Therapeutics (UT) Medical Monitor to discuss oral treprostinil dosing options.

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

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 re-started on study drug at a reduced dose or at 0.125 mg TID depending on the subject's clinical condition and 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.

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.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

This study is not blinded.

6.3 COMPLIANCE

The Investigator or other study site personnel under the direction of the Investigator will be responsible for dose titration of oral treprostinil and recording all dosing information in source documents. During telephone calls/emails, study site personnel will record the current dosing regimen of oral treprostinil and determine if the subject is taking oral treprostinil as prescribed. At the discretion of study site personnel, subjects may be provided with an optional dosing diary to help with study drug titration and accountability.

At scheduled study visits, subjects should be instructed to bring all study drug (including empty and unused bottles) to the study site. Upon return of study drug at each required protocol visit (eg, Weeks 6, 12, 18, 24, etc), the study coordinator or pharmacist must document the number of returned tablets of each strength and determine if the appropriate amount of study drug remains based upon the dose of study drug prescribed. Each subject will also be asked at each visit whether he or she has been compliant with dosing. 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, 24, etc), all bottles of study drug will be collected. Study drug returned will not be redispensed 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 at unscheduled visits.

7 EXPERIMENTAL PROCEDURES

7.1 TREATMENT PHASE

7.1.1 Baseline

All data collected at the subject's study termination visit during Study TDE-HF-301 and prior to initiating open-label study drug will serve as Baseline assessments for this study. Following completion of all TDE-HF-301 study termination assessments for a subject and entry of required data into the interactive voice or web response system (IVRS/IWRS), the study site personnel will be unblinded to that subject's treatment assignment. Subjects must sign an ICF and meet inclusion/exclusion criteria specific to this protocol.

The list of Baseline assessments are displayed below:

- Informed consent (prior to any study assessments)
- Inclusion/exclusion criteria
- Physical examination[a]
- Assessment of heart failure signs and symptoms with vital signs (following at least 5 minutes of rest [seated])[a]
- WHO Functional Class[a]
- AE assessment[a]
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the most recent dose of study drug from Study TDE-HF-301; Borg dyspnea score to be conducted immediately following 6MWT)[a]
- Urine pregnancy test (for WOCBP)[a]
- Clinical laboratory assessments[a]
- Plasma NT-proBNP[a]

---

[a] Assessments conducted during the study termination visit for Study TDE-HF-301 do not need to be repeated

- Study drug dosing (for subjects randomized to placebo in TDE-HF-301, the initial dose of oral treprostinil in TDE-HF-302 should be taken at the study site)
- Drug accountability
- Concomitant medications[a]
- Weekly telephone calls are highly recommended, especially after any dose changes

AEs that were ongoing at the end of the TDE-HF-301 study will be recorded as ongoing events for this open-label study. Concomitant medications that were ongoing at the TDE-HF-301 study termination visit will be recorded in the eCRF for the open-label study. The AEs and concomitant medications will be reported continuously for the duration of the study. Phone calls/emails to the subject must begin within 1 week of the subject receiving the first dose of study drug in this follow-up study and continue to be made weekly for the first 24 weeks of the study. After 24 weeks, phone calls/emails must be made at least monthly. Dose titration should occur as needed in accordance with Section 6.1.

7.1.2 Week 6 Visit

Subjects are to return to the study site at Week 6. This visit should be conducted within 7 days of the scheduled visit (as determined by the Baseline visit) and the following assessments are to occur:

- Assessment of heart failure signs and symptoms with vital signs (following at least 5 minutes of rest [seated])
- WHO Functional Class
- AE assessment
- 6MWT/Borg dyspnea score (6MWT to be initiated 3 to 6 hours after the most recent dose of oral treprostinil; Borg dyspnea score to be conducted immediately following 6MWT)
- Urine pregnancy test (for WOCBP)
- Oral treprostinil dose titration
- Dosing instructions/dosing/accountability
- Concomitant medications
- Weekly telephone calls/emails are highly recommended, especially after any dose changes

7.1.3 Week 12 Visit

Subjects are to return to the study site at Week 12. This visit should be conducted within 7 days of the scheduled visit (as determined by the Baseline visit). In addition to all assessments from the Week 6 visit, clinical laboratory assessments are to be conducted.

7.1.4 Week 18 Visit

Subjects are to return to the study site at Week 18. This visit should be conducted within 7 days of the scheduled visit (as determined by the Baseline visit) and all of the Week 6 visit assessments are to occur.

7.1.5 Week 24 Visit

Subjects are to return to the study site at Week 24. This visit should be conducted within 7 days of the scheduled visit (as determined by the Baseline visit). In addition to all assessments from the Week 6 visit, the following assessments are to be conducted:

- Clinical laboratory assessments
- NT-proBNP (NT-proBNP samples must be taken prior to the 6MWT)

7.1.6 Follow-up Visits (Every 12 Weeks)

Subjects should return to the study site every 12 weeks after the Week 24 visit. Follow-up visits are presented with the corresponding study week in Table 7-1. These visits should be conducted within 14 days of the scheduled visit (as determined by the Baseline visit). Assessment of AEs, concomitant medications, and dose titration should occur continuously between and during study visits. In addition to all assessments from the Week 6 visit, the following assessments are to be conducted:

- Clinical laboratory assessments[a]
- NT-proBNP[b] (Week 48 only [Follow-up Visit 2]; NT-proBNP samples must be taken prior to the 6MWT)

[a] To be assessed every 24 weeks
[b] To be assessed at Week 48 only (Follow-up Visit 2)

Table 7-1 Follow-up Visits by Week Beyond Week 24

Follow-up Visit	Corresponding Study Week[a]	Follow-up Visit	Corresponding Study Week[a]
#1	36	#19	252
#2	48	#20	264
#3	60	#21	276
#4	72	#22	288
#5	84	#23	300
#6	96	#24	312
#7	108	#25	324
#8	120	#26	336
#9	132	#27	348
#10	144	#28	360
#11	156	#29	372
#12	168	#30	384
#13	180	#31	396
#14	192	#32	408
#15	204	#33	420
#16	216	#34	432
#17	228	#35	444
#18	240	#36	456

[a] Visit window is ±14 days as determined by the Baseline visit.

7.1.7 Study Termination Visit

When subjects discontinue the study, they will complete a study termination visit. If possible, each subject should remain on study drug until they have completed the study termination visit. After the study termination visit is completed, subjects should down titrate the study drug over an appropriate period of time in accordance with their clinical condition. Once the study drug has been discontinued, any remaining supplies should be returned to the study site for drug accountability. In addition to all assessments from the Week 6 visit, the following assessments are to be conducted at the study termination visit:

- Physical examination
- Clinical laboratory assessments

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

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

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

When a subject is discontinued from the study, the Investigator will complete the study termination record and provide an explanation, if needed. If oral treprostinil has been administered, the Investigator should make every effort to perform all study termination evaluations prior to termination of oral treprostinil treatment.

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 or International Council for Harmonisation (ICH) Good Clinical Practices (GCP) guidelines
- The protocol is repeatedly violated or critical violations are documented
- Changes in personnel or facilities adversely affect performance of the study

9 ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a 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 a 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 Baseline.

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 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

AEs will be captured from the time the ICF is signed. Any AEs that are ongoing at the study termination visit from Study TDE-HF-301 should be recorded as continuing AEs in this open-label study. An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study

drug, and outcome is also to be documented in the eCRF (see Appendix 15.3 for definitions). Where possible, AEs should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically meaningful, or for at least 30 days if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. 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 UT 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. UT 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 UT 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 UT GDS. A follow-up SAE Notification Form must be forwarded to UT 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 3.3.2.4) are not to be reported to UT 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 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, with the exception of events attributable to the progression of the disease under study, which will only be reported if assessed as an SAE (see Section 3.3.2.4). 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 or 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

No formal sample size calculation has been conducted. All eligible subjects from Study TDE-HF-301 may enter this study.

10.3 ANALYSIS PLAN

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

The Safety population will be defined as all subjects in the study that received oral treprostinil at any time during the course of the study. All analyses will be performed on the Safety population. All AEs as recorded by the Investigators will be assigned Medical Dictionary for Regulatory Activities (MedDRA) preferred terms by the Sponsor for reporting purposes.

10.4 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

UT will supply oral treprostinil for administration during the study. Oral treprostinil tablets will be provided as 0.125-, 0.25-, 1-, and 2.5-mg strengths for the study. The oral treprostinil tablets are sustained release osmotic tablets. 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 of treprostinil (equivalent to 1.27 mg treprostinil diethanolamine), 2.5 mg of treprostinil (equivalent to 3.17 mg treprostinil diethanolamine). The 0.125-, 0.25-, 1-, and 2.5-mg tablets are colored blue, green, yellow, and pink, respectively. Oral treprostinil tablets will be provided in child resistant bottles each containing 100 tablets.

11.2 LABELING

Each bottle will be labeled in accordance with applicable national regulations, to include at least the following information: study drug, study reference code, strength, quantity, route of administration, manufacture or expiry date, lot number, Sponsor name, address and telephone number, and storage conditions. The labels on the bottles may include blank fields for 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 investigational medicinal product labeling or regulatory submissions for specific requirements by country or region in accordance with local regulations or guidance.

Study drug at the 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 bottle assigned to the subject at each study visit during the course of the study. Subjects should be instructed to return all study drug, including empty bottles, to the appropriate study personnel at every protocol-required visit.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

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

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records will be maintained during the study, and these records will include the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of unused drug 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 allowing 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 ICH GCP 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 authorized designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/EC-approved ICF prior to the conduct of any study-related activities. A copy of the signed ICF will be given to the subject, and the original will be retained in the study site's records.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each 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's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

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

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

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. UT, regulatory bodies, and the IRB/EC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/EC, or appropriate local regulatory agencies for purposes of

checking the accuracy of the data. A unique number will be assigned to all subjects and any report published will not identify the subjects by name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

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

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

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

13.2 STUDY DOCUMENTATION AND STORAGE

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

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH GCP guidelines, monitors for UT 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 must agree to allow the monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the monitor to discuss any findings or any relevant issues. In addition, auditors for UT or its designee may periodically contact the study site and conduct on-site visits.

14 REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002;166(1):111-117.

Bocchi EA, Bacal F, Auler Júnio JO, et al. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. Am J Cardiol. 1994;74(1):70-72.

Boilson BA, Schirger JA, Borlaug BA. Caveat medicus! Pulmonary hypertension in the elderly: a word of caution. Euro J Heart Failure. 2010;12:89-93.

Bonderman D, Ghio S, Felix SB, et al. Riociguat for the left ventricular systolic dynsfunction associated with pulmonary hypertension riociguat trial (LEPHT) study group. Circulation. 2013; 128(5):502-511.

Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized,double-blind, placebo-controlled, single-dose study. Chest. 2014; 146(5):1274-1211.

Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The flolan international randomized survival trial (FIRST). Am Heart J. 1997;134(1):44-54.

Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-Terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. CHEST. 2006;29:1313-1321.

Grossman NL, Fiack CA, Weinberg JM, et al. Pulmonary hypertension associated with heart failure and preserved ejection fraction: acute hemodynamic effects of inhaled iloprost. Pulm Circ. 2015; 5(1):198-203.

Guazzi M, Gomberg-Maitland M, Arena R, et al. Pulmonary hypertension in heart failure with preserved ejection fraction. J Heart Lung Transplant. 2015a; 34(3):273-281.

Guazzi M, Gomberg-Maitland M, Naeije R. Impact of pharmacologic interventions- treating endothelial dysfunction and group 2 pulmonary hypertension. Prog Cardiovasc Dis. 2015b; 57:473-479.

Guazzi M, Vicenzi M, Arena R. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011; 124(2):164-174.

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

Hussain N, Charalampopoulos A, Ramjug S, et al. Pulmonary hypertension in patients with heart failure and preserved ejection fraction:differential diagnosis and management. Pulmonary Circulation. 2016; 6(1):3-14.

Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: A randomized, controlled trial. Circulation. 2013; 127:624-633.

Kalra PR, Moon JCC, Coats AJS. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? Int J Cardiol. 2002;85(2-3):195-197.

Kaluski E, Cotter G, Leitman M, et al. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dyfunction, associated with secondary pulmonary hypertension – a multi-center randomized study. Cardiology. 2008;109(4):273-280.

Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: A community-based study. Am Coll Cardiol. 2009; 53(13):273-280.

Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007; 116(14):1555-1562.

Loh E, Stamler JS, Hare JM, et al. Cardiovascular effects of nitric oxide in patients with left ventricular dysfunction. Circulation. 1994;90:2780-2785.

Moraes DL, Colucci WS, and Givertz MM. Secondary pulmonary hypertension in chronic heart failure: The role of endothelium in pathology and management. Circulation. 2000; 102(14):1718-1723.

Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail. 2005;11(1):12-20.

Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27):2129-200.

Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309(12):1268-1277.

Rosenkranz S, Gibbs JS, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016; 37(12):942-954.

Serra W, Musiari L, Ardissino D, et al. Benefit of prostaglandin infusion in severe heart failure: preliminary clinical experience of repetitive administration. Int J Cardiol. 2011; 146(1):e10-15.

Simonneau G, Gartzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-D41.

Sueta CA, Gheorghiade M, Adams KF Jr, et al. Safety and efficacy of epoprostenol in patients with severe congestive heart failure: Epoprostenol multicenter research group. Am J Cardiol. 1995; 75(3):34A-43A.

Wu X, Yang T, Zhou Q, et al. Additional use of a phosphodiesterase 5 inhibitor in patients with pulmonary hypertension secondary to chronic systolic heart failure: a meta-analysis. Eur J Heart Fail. 2014; 16(4):444-453.

15 APPENDICES

15.1 PROCEDURE FOR 6-MINUTE WALK TEST AND BORG DYSPNEA SCORE

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 pre-measured 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 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 meaningful change from Baseline. If the results are determined to be a clinically meaningful 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 right heart catheterization [RHC]).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (eg, pre-planned operation which does not lead to further complications etc).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

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

Definitions of the causality categories are as follows:

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

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

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose or regimen of the study drug was not changed.
- Dose Increased – The dose or regimen of study drug was increased
- Dose 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
- Unknown – Changes to the administration of the study drug cannot be determined
- Not Applicable

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

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.

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

15.4 CLINICAL LABORATORY PARAMETERS

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

[a] Urine pregnancy test for WOCBP

Visit Test Schedule

Visit	Labs Collected
Baseline[b]	Chemistries, Hematology, NT-proBNP, urine pregnancy[a]
Week 6	Urine pregnancy[a]
Week 12	Chemistries, hematology, urine pregnancy[a]
Week 18	Urine pregnancy[a]
Week 24	Chemistries, hematology, NT-proBNP[c], urine pregnancy[a]
Follow-up visits[d]	Chemistries, hematology, NT-proBNP[e]
Study termination visit	Chemistries, hematology, urine pregnancy[a]

Abbreviation: NT-proBNP, N-Terminal pro-brain natriuretic peptide

[a] Urine pregnancy tests for WOCBP only

[b] Baseline clinical laboratory assessments for this study are those collected at Week 24 from study TDE-HF-301 and prior to initiation of treatment with open-label oral treprostinil

[c] NT-proBNP at Week 24 only

[d] During follow-up visits, clinical laboratory samples should be collected every 24 weeks

[e] NT-proBNP at Week 48 (Follow-up Visit 2) only

15.5 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, rhonci, 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)