A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

IND 70,362

Protocol RIN-PH-201

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	21 October 2015
Amendment 1	20 November 2015
Amendment 2	13 September 2016
Amendment 3	15 February 2017

LIST OF CONTACTS FOR STUDY

Study Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709
	[redacted] Clinical Trial Leader Telephone: [redacted] Fax: [redacted] [redacted]
	[redacted] Product Leader Telephone: [redacted] Fax: [redacted] [redacted]
	[redacted] Medical Monitor Telephone: [redacted] Fax: [redacted] [redacted]
	[redacted] SAE Phone: [redacted] SAE Fax: [redacted] [redacted]
Clinical Laboratory	[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease," protocol amendment 3 dated 15 February 2017 and agree to abide by all provisions set forth therein.

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

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the 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 inhaled treprostinil and acknowledge that review of the information contained in the Investigator's Brochure is a requirement for Investigators before using inhaled treprostinil in a clinical study.

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease
Study Phase	Phase II/III
Indication	Pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE)
Primary Objective	To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE
Primary Endpoint	To evaluate the change in 6-minute walk distance (6MWD) measured at peak exposure from Baseline to Week 16
Secondary Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD from Baseline to Week 12 2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16 3. Change in trough 6MWD from Baseline to Week 15
Exploratory Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD from Baseline to Week 4 2. Change in peak 6MWD from Baseline to Week 8 3. Change in quality of life (QOL) as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16 4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met: a. Hospitalization due to a cardiopulmonary indication

	b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart c. Death (all causes) d. Lung transplantation 5. Change in distance saturation product (DSP) from Baseline to Week 16 6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16 7. Optional evaluation of whole genome sequence at Baseline
Safety Endpoints	1. Adverse events (AEs) 2. Oxygenation a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2]) b. Supplemental oxygen requirement (L/min) 3. Pulmonary function: a. Forced expiratory volume in 1 second (FEV1) b. Forced vital capacity (FVC) c. Total lung capacity (TLC) d. Lung diffusion capacity (DLCO) 4. Clinical laboratory parameters 5. Vital signs 6. Electrocardiograms (ECG) 7. Hospitalization due to a cardiopulmonary indication 8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Study Design	Multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study
Sample Size	Approximately 314 subjects at approximately 120 centers

Summary of Subject Eligibility Criteria	Inclusion criteria: 1. Subject voluntarily gives informed consent to participate in the study. 2. Males and females aged 18 years or older at the time of informed consent. a. Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will: i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or ii. Use 2 medically acceptable, highly-effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug. b. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug. 3. The subject has a confirmed diagnosis of World Health Organization (WHO) Group 3 PH based on computed tomography (CT) imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomization. Subjects may have any form of ILD or CPFE. 4. Subjects are required to have a right heart catheterization (RHC) within 1 year prior to randomization with the following documented parameters: a. Pulmonary vascular resistance (PVR) > 3 Wood Units (WU) and b. A pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg and c. A mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg 5. Baseline 6MWD ≥ 100 meters

6. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization.
7. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.
8. Subjects with connective tissue disease (CTD) must have a Baseline FVC of < 70%.

Exclusion criteria:

1. The subject has a diagnosis of pulmonary arterial hypertension (PAH) or PH for reasons other than WHO Group 3 PH-ILD as outlined in inclusion criterion 3.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any PAH approved therapy including: prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE5-I), or soluble guanylate cyclase (sGC) stimulator within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
    a. PCWP > 15 mmHg
    b. Left ventricular ejection fraction < 40%.

    Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) will not be excluded.
5. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.

	6. Current use of any inhaled tobacco/marijuana products or a significant history of drug abuse at the time of informed consent. 7. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization. 8. Initiation of pulmonary rehabilitation within 12 weeks prior to randomization. 9. In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity) that would likely be the primary limit to ambulation (as opposed to PH). 10. Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomization. 11. Severe concomitant illness limiting life expectancy (< 6 months). 12. Acute pulmonary embolism within 90 days of randomization.
Drug Dosage and Formulation	Inhaled treprostinil (6 mcg/breath) or placebo Treatment Phase: All subjects will initiate inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated.
Control Group	Placebo
Route of Administration	Inhaled

Procedures	Subjects will be assessed during Screening and Baseline to determine eligibility for the study. Once eligible, 5 Treatment Phase visits to the clinic will be required at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit). An Early Termination (ET) Visit will be conducted for subjects who end treatment prior to Week 16; all assessments planned for the final Week 16 Visit will be conducted during the ET Visit, as applicable. Subjects will also be contacted at least weekly by telephone or email to assess tolerance to study drug, AEs, and changes to concomitant medications. Key Assessments: • Pregnancy test: Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit or ET. • Blood for NT-proBNP and clinical labs will be obtained at Baseline, Week 8, and Week 16 or ET. • A peak 6-minute walk test (6MWT) will be conducted at Baseline, Week 4, Week 8, Week 12, and Week 16 or ET. • A trough 6MWT will be performed at Week 15 (at least 24 hours prior to the Week 16 6MWT). • Pulse oximetry will be performed immediately prior to, during, and immediately after each 6MWT. • Pulmonary function tests (PFTs) will be conducted at Baseline, Week 8, and Week 16 or ET. • SGRQ will be completed at Baseline and Week 16 or ET. • An optional blood sample will be collected for whole genome sequencing at Baseline. • An optional blood sample will be collected for the analysis of biomarkers (specific targets to be determined) at Baseline and Week 16 or ET. • An ECG will be conducted at Baseline and Week 16 or ET. • Hospitalizations due to cardiopulmonary indications and exacerbations of underlying lung disease will be evaluated from the time of informed consent until study discontinuation.

	• Time to clinical worsening will be evaluated from the time of randomization until study discontinuation.
Statistical Considerations	Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD measured at peak exposure assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%. The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. The clinical hypothesis is that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between 2 treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.
Sponsor	United Therapeutics Corp. 55 TW Alexander Drive P.O. Box 14186 Research Triangle Park, NC 27709 United States of America

TABLE OF CONTENTS

Table of In-Text Tables

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 (PVR). The World Health Organization (WHO) classifies PH due to lung diseases and/or hypoxemia as WHO Group 3 PH (Simonneau 2009). This classification includes PH due to interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).

Interstitial lung disease encompasses a heterogeneous group of parenchymal lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs within the lungs (Travis 2013, Seeger 2013). Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs. The symptomatology of ILD is non-specific, and covers a wide range of symptoms, whose severity can vary substantially among patients. The incidence of PH in ILD has been reported in up to 86% of patients and is associated with a poorer prognosis and decreased quality of life (QOL) (Nathan 2008, Nathan 2013).

Combined pulmonary fibrosis and emphysema is characterized by emphysema, fibrosis, and abnormalities of gas exchange (Jankowich 2012). Up to 50% of CPFE patients have been reported to develop PH with increased PVR associated with a decreased survival (Cottin 2010, Seeger 2013).

There are no approved treatments for PH in patients with ILD or CPFE; however, the results of some approved therapies for pulmonary arterial hypertension (PAH) have stimulated further investigation in these indications (Seeger 2013, Saggar 2014, Agarwal 2015, Roccia 2013).

1.2 INHALED TREPROSTINIL BACKGROUND

1.2.1 General Pharmacology

Treprostinil, 2-[[(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid, is a chemically stable tricyclic analogue of prostacyclin. The pharmacology of treprostinil is well-characterized and approved for the

treatment of PAH following either the subcutaneous (SC), intravenous (IV), inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

Prostacyclin is known to lower pulmonary artery pressure, increase cardiac output without affecting the heart rate (HR), improve systemic oxygen transport and possibly reverse pulmonary arterial remodeling. There is increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells, along with vasodilation, may contribute to the therapeutic effects of prostacyclin in the treatment of PAH. Treprostinil acts by triggering direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induced concentration dependent relaxation of rabbit isolated pre-contracted mesenteric arteries and inhibited 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. The mechanism of action of treprostinil is therefore likely to be multifactorial.

Treprostinil for inhalation (Tyvaso®) is approved in the United States, Argentina, and Israel for the treatment of PAH (WHO Group 1) in patients with New York Heart Association (NYHA) Functional Classification III symptoms, to increase exercise ability.

1.2.2 General Toxicology

A well-defined clinical safety profile exists for treprostinil sodium; acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies have been performed in both rats and dogs and support the chronic administration to patients (Remodulin® Package Insert 2014).

The toxicokinetic profile of treprostinil was also evaluated in acute and repeat dose toxicity studies of up to 13 weeks in duration in rodents and dogs which supported the chronic administration of inhaled treprostinil to patients. In addition, a 2-year rat carcinogenicity study was performed with treprostinil inhalation at target doses up to 5.26, 10.6, and 34.1 mcg/kg/day which found no evidence for carcinogenic potential associated with inhaled treprostinil in rats at systemic exposure levels up to 35 times the clinical exposure at the target

maintenance dose of 54 mcg. Refer to the inhaled treprostinil Investigator's Brochure for a full description of nonclinical data.

1.2.3 Clinical Experience

A series of acute and chronic investigator-initiated clinical studies were conducted with inhaled treprostinil to optimize the formulation for inhalation, determine dose response, tolerability, and safety and also to evaluate safety and tolerability when combined with other PAH therapies (Channick 2006, Voswinckel 2006). In the acute dosing studies, administration of inhaled treprostinil resulted in pulmonary vasodilation at relatively low doses. In the chronic studies, administration of inhaled treprostinil resulted in sustained improvement of exercise capacity.

A randomized, double blind, placebo controlled, Phase III study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil in combination with approved PAH therapies. Two hundred and thirty-five subjects who were clinically stable on an approved background oral PAH therapy (bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by 6-minute walk distance (6MWD). At Week 12, subjects receiving inhaled treprostinil had a median improvement of +21.6 meters in 6MWD and subjects in the placebo group had a median improvement of +3.0 meters. The Hodges-Lehmann placebo-corrected median change from baseline in peak 6MWD was +20.0 meters (p=0.00044). The durability of this result was supported by secondary measures related to the trough 6MWD, which was measured at least 4 hours after the last dose of inhaled treprostinil. At Week 12, trough 6MWD showed a placebo-corrected median treatment effect of 13.7 meters (p=0.0066). The most commonly reported adverse events (AEs) in the inhaled treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment-related changes in vital signs, physical examination (PE) findings, chest x-rays, pulmonary function tests (PFTs), or clinical laboratory parameters (McLaughlin 2010).

An open-label, extension study of the TRIUMPH-I study to evaluate the use of long-term inhaled treprostinil therapy was also conducted (TRIUMPH-OL). Subjects received 1 to

12 breaths (6 to 72 mcg) 4 times daily to achieve daily doses of 24 to 288 mcg. The longest duration of inhaled treprostinil exposure in the open-label study was 5.4 years and the mean duration 2.3 years. There were observed improvements in median 6MWD at 6, 12, 18, and 24 months of 28, 31, 32, and 18 meters, respectively. These data support the durability of improvement in 6MWD obtained with inhaled treprostinil as demonstrated during the double-blind phase of the study. Therapeutic benefit was also noted with improvements in the Borg dyspnea score, NYHA Functional Classification, and QOL. Survival was robust with 1 and 2 year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the study. The most frequently reported AEs during the open-label study were cough (39%), headache (31%), upper respiratory tract infection (22%), and nausea (22%). There were no clinically significant changes in clinical chemistry or hematology parameters. Unique findings that related to the inhaled route of administration, in addition to cough, were throat pain and throat irritation, occurring in 12% and 10% of subjects, respectively. These events were usually of mild or moderate severity and transient in duration. In a few subjects, these specific AEs were more pronounced as 6 subjects (3%) discontinued inhaled treprostinil due to cough, including 1 subject (<1%) with dry throat (Benza 2011).

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Inhaled treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in patients with WHO Group 1 PH (McLaughlin 2010). Inhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity (Seeger 2013).

The use of inhaled prostacyclin therapy in patients with WHO Group 3 PH has been recently evaluated. In particular, Wang and colleagues (Wang 2015) reported data on 67 chronic obstructive pulmonary disease (COPD) patients with PH and found no change in arterial blood gases when a single dose of iloprost was administered during right heart catheterization (RHC). In addition, Bajwa and colleagues recently completed a prospective 16-Week study in 9 COPD subjects with PH which reported no notable changes in arterial blood gases over the 16-Week treatment period (Bajwa 2016). Finally, Agarwal and colleagues (Agarwal

2015) recently presented data on 35 patients with WHO Group 3 PH who received treatment with inhaled treprostinil for 6 months. This retrospective review reported a mean increase from baseline in 6MWD of 61 meters with obstructive and restrictive patients reporting mean increases of 71 meters and 50 meters, respectively. Notably, this study also found that inhaled treprostinil was well tolerated with cough being the most commonly reported AE. Data from these recently completed pilot studies suggest that inhaled treprostinil can be safely administered in patients with WHO Group 3 PH.

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE.

2 OBJECTIVES

To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE.

2.1 PRIMARY ENDPOINT

To evaluate the change in 6MWD measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

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

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

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

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD from Baseline to Week 8
3. Change in QOL as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Time to clinical worsening from the time of randomization until 1 of the following criteria are met:

   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
5. Change in distance saturation product (DSP) from Baseline to Week 16
6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16
7. Optional evaluation of whole genome sequence at Baseline

2.4 SAFETY ENDPOINTS

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

1. AEs
2. Oxygenation
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO2])
   b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
   a. Forced expiratory volume in 1 second (FEV1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalization due to a cardiopulmonary indication
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study. Subject eligibility will be based on inclusion and exclusion criteria described in Section 4. Approximately 314 eligible subjects will be randomized to study treatment in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤ 350 meters and > 350 meters). Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo screening assessments as described in Sections 7.1 and 7.3. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6-minute walk test (6MWT) used to confirm eligibility criteria must be performed prior to randomization.

Baseline Visit: The Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments (Sections 7.2 and 7.3), be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6MWT used to confirm eligibility criteria must be performed prior to randomization.

Treatment Phase: The Treatment Phase consists of 5 study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit; at least 24 hours after the Week 15 Visit). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

A schedule of visits and assessments is presented in Section 3.2.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
Study Day	**-30 to -1**	**1**	**1**	**29**	**57**	**85**	**106**	**113**	
Informed Consent	X		X						
Subject Eligibility[c]	X	X	X						
Pre-Baseline Review Form[c]	X		X						
Medical History with PH History and Demographics	X		X						
SGRQ		X	X					X	X
Physical Examination	X		X					X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments	X	X	X		X			X	X
NT-proBNP[e]		X	X		X			X	X
Blood Sample for Biomarker Evaluation (Optional)[f]		X	X					X	X
Blood Sample for Whole Genome Sequencing (Optional)[g]		X	X						
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
12-Lead ECG		X	X					X	X
6MWT[i]	X	X	X	X	X	X		X	X
Trough 6MWT[j]							X		
Pulse Oximetry[k]	X	X	X	X	X	X	X	X	X
Documentation of Supplemental Oxygen Requirement	X	X	X	X	X	X	X	X	X
PFTs[l]		X	X		X			X	X
Randomization		X	X						
Device Training		X	X						
Dosing instructions / Dosing / Dosing Diary / Accountability		X[r]	X[r]	X	X	X	X	X	X
Weekly Telephone / Email Contact[m]		X--	X--	--X--	--X--	--X--	--X--	--X	
Adverse Events[n]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Concomitant Medications	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Hospitalization due to a cardiopulmonary indication[o]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Exacerbations of Underlying Lung Disease[p]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
Time to Clinical Worsening[q]		X--	--X--	--X--	--X--	--X--	--X--	--X	X

Abbreviations: ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFTs, pulmonary function tests; PH, pulmonary hypertension; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; CT, computed topography; SpO_2, saturation of peripheral capillary oxygenation; HR, heart rate; eCRF, electronic case report form; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, lung diffusion capacity; AE, adverse event; SAE, serious adverse event; 6MWD, 6-minute walk distance; ET, early termination

[a] Screening Visit assessments can occur up to 30 days prior to the first dose of study drug. Baseline assessments can occur up to 48 hours prior to the first dose of study drug to allow for scheduling of all activities; however, the Baseline 6MWT must be performed prior to randomization. Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs, 6MWT, and CT scan (if a historical scan within 6 months is not available) assessments used to determine eligibility criteria must be performed prior to randomization. Sites should provide a completed Pre-Baseline review form to the Medical Monitor which will be reviewed, signed, and returned to the site prior to randomization.

[b] The visit window for Week 4, Week 8, Week 12, Week 15, and Week 16 is ± 5 days. The Week 16 visit must occur at least 24 hours after the Week 15 visit.

[c] For the Screening and Baseline Visits, the subject must be evaluated for and meet all inclusion/exclusion criteria.

[d] 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 recovery from the 6MWT.

[e] Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT and will occur prior to randomization at Baseline (or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined).

[f] For subjects consenting to the optional biomarker sample.

[g] For subjects consenting to the optional whole genome sequencing sample.

[h] For females of childbearing potential.

[i] If the subject has not previously undergone a 6MWT at the study site on the course intended for use during the study, a practice test must be conducted at the Screening Visit and must precede the Baseline 6MWT by at least 1 day. The Baseline 6MWT must precede randomization. The Week 4, Week 8, Week 12, and Week 16 peak 6MWT must occur within 10 to 60 minutes after the most recent study drug dose. 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 at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[j] The Week 15 trough 6MWT must occur at least 4 hours after the most recent study drug dose and at least 24 hours prior to the Week 16 6MWT. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[k] Pulse oximetry will be performed immediately prior to, during, and immediately following each 6MWT. Pulse oximetry will include the measurement of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the eCRF. In addition, the lowest recorded SpO_2 obtained during each 6MWT will be recorded in the eCRF.

[l] PFTs will include the evaluation of FEV1, FVC, TLC, and DLCO. Baseline PFTs must be performed prior to randomization. PFTs should be performed after recovering from the Baseline, Week 8, and Week 16 or ET 6MWTs.

[m] At least weekly telephone contact is required throughout the study (may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in clinic for clinically significant AEs or other emergent issues.

[n] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed and should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit (Week 16).

[o] Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration, should also be recorded as SAEs per Appendix 15.2.

[p] Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (see Section 3.3.2.10). Exacerbations will also be recorded as AEs or SAEs per Appendix 15.2.

[q] Time to clinical worsening will be measured from the time of randomization until 1 of the following criteria are met: hospitalization due to a cardiopulmonary indication; decrease in 6MWD > 15% from Baseline directly related to the disease under study, at 2 consecutive visits and at least 24 hours apart; death (all causes); or lung transplantation.

[r] Once all entry criteria have been met and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (Defined as Day 1).

[s] Subjects who permanently discontinue study drug during the 16-week Treatment Phase are encouraged to undergo premature termination assessments prior to discontinuing study drug and are required complete all remaining scheduled study visits through Week 16 (excluding the Week 15 Visit) to be eligible for entry into the open-label study.

[t] The premature termination of study drug visit should be conducted prior to study drug discontinuation or as close as possible to the last dose of study drug.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 6-Minute Walk Test

The 6MWT is a validated and reliable measure of exercise capacity in patients with chronic respiratory diseases (Holland 2014). This study will utilize an unencouraged 6MWT to minimize potential bias associated with encouragement. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements as described in Appendix 15.1. Prior to the start of each 6MWT the subject must rest (seated) for at least 10 minutes. This 6MWT protocol applies to the practice (if applicable), Baseline, and treatment 6MWTs. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. Pulmonary rehabilitation may not be introduced to a subject's treatment regimen between randomization and Week 16 or until the permanent discontinuation of study drug. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.1 Practice 6-Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course intended for use during the study. Subjects who have not previously performed the 6MWT at the study site on the course intended for use during the study, must perform a practice 6MWT at the study site at least 1 day prior to the Baseline Visit.

3.3.1.1.2 Baseline 6-Minute Walk Test

The Baseline 6MWT must be performed prior to randomization. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

Note: The Baseline 6MWT (not the practice 6MWT) will determine the subject's eligibility to participate in the study (6MWD $\geq$ 100 meters per inclusion criteria).

3.3.1.1.3 Treatment 6-Minute Walk Tests

3.3.1.1.3.1 Peak 6-Minute Walk Tests

Peak 6MWTs will be conducted at Weeks 4, 8, 12, and 16 or Early Termination (ET). The 6MWT must be conducted between 10 to 60 minutes after the most recent dose of study drug. If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate at all subsequent 6MWT assessments. The Week 16 peak 6MWT should occur at least 24 hours after the Week 15 Visit. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.3.2 Trough 6-Minute Walk Test

A trough 6MWT will be performed during the Week 15 Visit. The trough 6MWT must be performed at least 4 hours after the most recent dose of study drug and at least 24 hours prior to the Week 16 6MWT. If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate at all subsequent 6MWT assessments. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

Subjects who discontinue study drug prematurely prior to the Week 15 Visit do not need to return to the clinic for the Week 15 Visit to be eligible for participation in the open-label extension study (Section 7.8).

3.3.1.2 St. George's Respiratory Questionnaire

The SGRQ will be conducted at Baseline (prior to study drug) or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined and at Week 16 (or ET for those subjects discontinuing study drug/study prematurely). The SGRQ should be completed as the first assessment during these visits (after informed consent is obtained) before the subject completes any of the other scheduled visit assessments. A copy of the SGRQ can be found in Appendix 15.3.

3.3.1.3 N-terminal Pro-brain Natriuretic Peptide

Plasma NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). NT-proBNP sample collection will occur at Baseline (or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined) prior to starting study drug, Week 8, and Week 16 or ET. Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT.

3.3.1.4 Time to Clinical Worsening

Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:

a. Hospitalization due to a cardiopulmonary indication
b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
c. Death (all causes)
d. Lung transplantation

Because there are no Food and Drug Administration (FDA) approved therapies for the treatment of WHO Group 3 PH, subjects experiencing clinical worsening may remain on study therapy for the duration of the study (or until criteria for study termination are met per Section 8.1 of the protocol). However, if a subject is removed from study therapy due to clinical worsening, the subject must return to the clinic for regularly scheduled study visits (excluding the Week 15 Visit) to be eligible for the open-label extension study (Section 7.8). Subjects experiencing death or lung transplantation will be discontinued from the study per Section 8.1 of the protocol.

3.3.1.5 Change in Distance Saturation Product

Change in DSP is the product of distance walked and lowest SpO_2 recorded during the 6MWT. This assessment has been shown to be predictive of mortality in patients with idiopathic pulmonary fibrosis and as such will be evaluated as an exploratory endpoint in this study (Lettieri 2006). Change from Baseline to Week 16 or ET in DSP will be calculated.

3.3.1.6 Optional Biomarker

For subjects consenting to the optional biomarker sample, blood will be collected for the evaluation of biomarkers (specific targets to be determined) at Baseline and at Week 16 or ET.

3.3.1.7 Optional Whole Genome Sequencing

For subjects consenting to whole genome sequence analysis, a blood sample will be collected at Baseline. These samples will be shipped to the central laboratory for processing and storage prior to analysis. Whole genome sequences will be analyzed for genetic makers that may be associated with clinical response and tolerability.

3.3.2 Safety

During this study, treatment emergent changes in PE findings, vital signs, clinical laboratory parameters, ECG parameters, PFTs, oxygenation, and the development of AEs after treatment will be the primary assessments of safety. Hospitalizations due to cardiopulmonary indications will also be recorded from the time of informed consent until study termination (or ET for those subjects discontinuing the study prematurely). Exacerbations of underlying lung disease will also be recorded from the time of informed consent until study termination.

3.3.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PH history, and PE will be conducted during Screening. If any changes to the medical history occur between the Screening and Baseline Visit, those should be recorded. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs should be recorded. Any significant changes to the subject's medical condition and PE must be documented throughout the course of the study. A complete PE will also be conducted by appropriate study personnel (as documented on the Delegation of Authority Log) at the Week 16 or ET Visit. Any clinically significant changes from Baseline noted during the Week 16 or ET PE should be reported as AEs.

3.3.2.2 Vital Signs

Vital signs will be assessed at Screening, Baseline, and each subsequent study visit or ET. Vital signs measured will include blood pressure (systolic and diastolic), HR, respiratory rate

(RR), temperature, and weight. Height will be assessed at Screening only. Vital signs must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. 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, they should be obtained after recovery of the 6MWT. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms.

3.3.2.3 12-Lead Electrocardiogram

A 12-lead ECG will be recorded after at least 5 minutes of rest in the semi-recumbent position at Baseline (prior to study drug) and repeated at the Week 16 or ET Visit. Recordings should include lead II as a rhythm strip and contain at least 5 QRS complexes. ECG parameters to be collected include rhythm, HR, PR interval, QT interval, QRS duration, and any clinically significant abnormalities.

3.3.2.4 Clinical Laboratory Assessments

The results of all clinical laboratory tests conducted at Screening and Baseline must be assessed by the Investigator to determine each subject's eligibility to participate in the study prior to starting study drug. Screening and Baseline clinical laboratory assessments can be combined into a single blood draw if all eligibility criteria are met within 48 hours prior to the first dose of study drug at Baseline. Central laboratory data are ultimately used to qualify subjects for the study. However, for subjects who are well known to the Investigator and who are clinically stable, the Investigator may confirm eligibility using local laboratory values so as not to delay randomization while waiting for central laboratory results if the Screening and Baseline Visits are combined.

Clinical laboratory results outside the normal reference range must be assessed for clinical significance by the Investigator. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status.

Clinically significant abnormal laboratory test values will be reported as AEs and treated and/or followed-up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator. Where appropriate, medical tests and examinations will be performed to assess and document resolution.

3.3.2.4.1 Clinical Chemistry and Hematology

Blood for the measurement and evaluation of clinical chemistry and hematology, will be collected at the Screening and Baseline Visits prior to administration of study drug and repeated at Week 8 and Week 16 or ET to assess for treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Values for the following parameters will be obtained:

Electrolyte Panel
- Sodium
- Potassium
- Bicarbonate
- Chloride

Chemistry Panel
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Urea nitrogen
- Creatinine
- Calcium
- Albumin

Hematology Panel
- Hemoglobin
- Hematocrit
- Red blood cell count
- Red blood cell morphology
- White blood cell count
- Platelet count

3.3.2.4.2 Pregnancy Testing

Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and each subsequent study visit (or Baseline Visit if the Screening and Baseline Visits are combined) or ET. A positive pregnancy test will exclude the subject from further participation in the study. Pregnant subjects who are discontinued from the study will be transitioned to an alternate therapy at the discretion of the Investigator.

3.3.2.5 Pulmonary Function Tests

Pulmonary Function Tests will be assessed at Baseline and repeated at Week 8 and Week 16 or ET. Baseline PFTs are to be conducted prior to randomization and after recovery from the 6MWT. The Week 8 and Week 16 or ET PFTs should be conducted after recovery from the 6MWT. If the PFTs are done both prior to and after a bronchodilator, only the pre-bronchodilator values will be recorded.

The following parameters will be recorded (absolute values and % predicted): FEV1, FVC, TLC, and DLCO (uncorrected for hemoglobin and lung volume).

3.3.2.6 Oxygenation

3.3.2.6.1 Pulse Oximetry

Pulse oximetry will be assessed immediately prior to, throughout the conduct of, and immediately after each scheduled 6MWT assessment at Baseline, Week 4, Week 8, Week 12, Week 15, and Week 16 or ET. Pulse oximetry will also be performed at Screening during the practice 6MWT assessment as applicable. Pulse oximetry will include the collection of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the electronic case report form (eCRF). In addition, the lowest recorded SpO_2 obtained during each 6MWT will be recorded in the eCRF.

When possible, pulse oximetry should be recorded using the provided pulse oximeter (Nonin 3150). In the event the provided pulse oximeter cannot be used (ie, subject has known issues with obtaining accurate readings from a finger probe, etc) an alternative device may be used with prior Sponsor approval so long as the same device is used for all planned 6MWT.

3.3.2.6.2 Supplemental Oxygen Requirement

The amount of supplemental oxygen (L/min) required at rest will be assessed at Baseline and at regularly scheduled visits or ET. The amount of supplemental oxygen required at the 6MWT assessment will also be recorded for each 6MWT assessment.

3.3.2.7 Adverse Events

Adverse events will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed. Each subject will be questioned for AEs at each scheduled study visit and during required telephone/email contacts. Subjects will also be instructed to spontaneously report all AEs throughout the study.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for serious (ie, serious adverse events [SAEs]) should be followed until resolution, death, or the

subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final study visit (Week 16 or ET). All AEs/SAEs that occur while the subject is in study will be recorded as instructed in this protocol.

Sections 9 and 15.2 provide the guidelines and definitions for recording AEs.

3.3.2.8 Concomitant Medications

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

3.3.2.9 Hospitalization due to Cardiopulmonary Indications

Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration should also be recorded as SAEs per Appendix 15.2. Please note that, when possible, study medication should be continued during hospitalizations.

3.3.2.10 Exacerbations of Underlying Lung Disease

An exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (Collard 2016). As adapted from the publication by Collard and colleagues (Collard 2016), the following diagnostic criteria may be used to help support a diagnosis of acute exacerbation:

1. Previous or concurrent diagnosis of ILD including CPFE
2. Acute worsening or development of dyspnea typically of less than 1 month duration
3. Computed topography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
4. Deterioration not fully explained by cardiac failure or fluid overload

For the purposes of this protocol, events that are clinically considered to meet the definition of acute exacerbation but fail to meet all 4 diagnostic criteria due to missing CT data should still be considered an exacerbation for reporting purposes.

Exacerbations of underlying lung disease should be recorded throughout the duration of the study from the time of informed consent until study termination. Exacerbations of underlying lung disease will also be reported as AEs or SAEs per Appendix 15.2.

3.3.2.11 Weekly Telephone/Email Contact

Weekly telephone/email contact is required throughout the 16-week study to instruct the subject to titrate their dose of study drug and to assess for AEs and concomitant medications. Weekly telephone/email contact 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). The subject may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All telephone or email contacts (ie, any dosing instructions, AEs reported and/or medication changes) with the subject must be noted in the source documentation.

3.4 NUMBER OF SUBJECTS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

3.5 NUMBER OF CENTERS

This study is multicenter with approximately 120 participating study centers.

3.6 ESTIMATED STUDY DURATION

From Screening until study completion, expected duration of study participation is approximately 20 weeks (includes a 4-week Screening period and 16-week Treatment Phase).

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during the Screening period and reconfirmed at the Baseline Visit prior to the first dose of study drug. Study related procedures must be conducted during the Screening period after obtaining informed consent to determine subject eligibility for the study.

4.1 INCLUSION CRITERIA

1. Subject voluntarily gives informed consent to participate in the study.
2. Males and females aged 18 years or older at the time of informed consent.
   a. Females of reproductive potential[1] must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will:
      i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
      ii. Use 2 medically acceptable, highly-effective forms of contraception[2] for the duration of study, and at least 30 days after discontinuing study drug.
   b. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. The subject has a confirmed diagnosis of WHO Group 3 PH based on CT imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomization. Subjects may have any form of ILD or CPFE.
4. Subjects are required to have a RHC within 1 year prior to randomization with the following documented parameters:
   a. Pulmonary vascular resistance (PVR) > 3 Wood Units (WU) and
   b. A pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg and
   c. A mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg
5. Baseline 6MWD ≥ 100 meters.
6. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization.
7. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.
8. Subjects with connective tissue disease (CTD) must have a Baseline FVC of < 70%.

4.2 EXCLUSION CRITERIA

1. The subject has a diagnosis of PAH or PH for reasons other than WHO Group 3 PH-ILD as outlined in inclusion criterion 3.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.

---

[1] Females who are successfully sterilized (surgical sterilization methods include hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (defined as amenorrhea for at least 12 consecutive months) are not considered to be of reproductive potential.

[2] Medically acceptable, highly-effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), and barrier methods (such as a condom or diaphragm) when used with a spermicide. For women of reproductive potential, a negative pregnancy test is required at Screening and Baseline prior to initiating study drug.

3. The subject has received any PAH approved therapy including: prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE5-I), or soluble guanylate cyclase (sGC) stimulator within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
   a. PCWP > 15 mmHg
   b. Left ventricular ejection fraction < 40%.

Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) will not be excluded.

5. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
6. Current use of any inhaled tobacco/marijuana products or significant history of drug abuse at the time of informed consent.
7. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization.
8. Initiation of pulmonary rehabilitation within 12 weeks prior to randomization.
9. In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity) that would likely be the primary limit to ambulation (as opposed to PH).
10. Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomization.
11. Severe concomitant illness limiting life expectancy (< 6 months).
12. Acute pulmonary embolism within 90 days of randomization.

4.3 PRESCRIBED THERAPY

Subjects must not be receiving any prostacyclin (ie, epoprostenol, treprostinil, iloprost, beraprost, or any other prostacyclin therapy) within 60 days prior to randomization (unless used for acute vasoreactivity testing) until study termination. Subjects must also not be receiving any other FDA approved PAH background therapies including: an IP receptor agonist, ERA, PDE5-I, and/or sGC stimulator within 60 days of randomization through the permanent discontinuation of study drug or study termination.

Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization. Subjects may

not newly initiate pirfenidone or nintedanib from randomization through the permanent discontinuation of study drug or study termination.

Subjects may not initiate pulmonary rehabilitation (rehab) within 12 weeks prior to randomization until the permanent discontinuation of study drug or study termination.

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, should be recorded in the subject's source documents and transcribed into the eCRF as required. The flow rate of supplemental oxygen should be recorded as outlined in Section 3.3.2.6.2.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo.

5.2 RANDOMIZATION

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo. An IXRS will be utilized for the central randomization procedure. Sites will enter values of the qualifying 6MWT and the date the test was conducted into the IXRS and will be notified if the subject qualifies for the study.

All subjects will be randomized using a centrally administered stratified permuted block randomization, stratified by Baseline 6MWD ($\leq$ 350 meters and > 350 meters).

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

5.3 BLINDING

The Investigator, study site, subject and Sponsor will not be aware of the treatment allocation. All clinical study material will be provided as blinded study drug.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Placebo will be provided as an identical solution that will be inhaled using the same ultrasonic nebulizer. All subjects will receive study drug (inhaled treprostinil or placebo) using the commercially available TD-100 ultrasonic nebulizer (Tyvaso Inhalation System®). Subjects will be trained on inhalation of study drug using the nebulizer device. Detailed instructions for the use of these devices will be provided to all study subjects. In addition, all subjects will receive a copy of the commercially available Tyvaso Inhalation System Instructions for Use (IFU) for the TD-100 ultrasonic nebulizer.

Once informed consent has been signed, all entry criteria have been met, and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (defined as Day 1). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily within 4 weeks of beginning the treatment, as clinically tolerated. Table 6-1 provides a guideline for the recommended dose escalations.

Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table

Study Day[a]	Single Dose	Total Daily Dose
Titrating to maximum dose of 12 breaths		
1-3	3 breaths QID (18 mcg)	72 mcg
4-6	4 breaths QID (24 mcg)	96 mcg
7-9	5 breaths QID (30 mcg)	120 mcg
10-12	6 breaths QID (36 mcg)	144 mcg
13-15	7 breaths QID (42 mcg)	168 mcg
16-18	8 breaths QID (48 mcg)	192 mcg
19-21	9 breaths QID (54 mcg)	216 mcg
22-24	10 breaths QID (60 mcg)	240 mcg
25-27	11 breaths QID (66 mcg)	264 mcg
28 (and beyond)	12 breaths QID (72 mcg)	288 mcg

Abbreviations: QID, 4 times daily; mcg,: micrograms
[a] Study day refers to the days on study drug with Day 1 referring to the first dose of study drug.

The dosing schedule is recommended as a guide only. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and functional improvement.

If subjects are unable to tolerate the initial 3 breaths, they may decrease their next dose to 1 or 2 breaths of study drug (as determined by the Investigator) 4 times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of 3 breaths, and titrate to a target dose of 9 breaths and a maximum dose of 12 breaths 4 times a day during waking hours, as clinically tolerated.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject should occur prior to each dose adjustment or at least weekly to monitor for AEs, clinical worsening events, and make decisions about dose titration.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, the site personnel, subject, and Sponsor will remain blinded to the treatment assignment of all subjects. A medical emergency (eg, a life threatening event) constitutes the only reason for unblinding during the Treatment Phase. Appropriate communications must take place between the site and the Sponsor before accessing the IXRS to allow unblinding of a subject's treatment assignment.

6.3 COMPLIANCE

Each subject will be provided with a dosing diary in order to record dosing information from randomization until Week 16. Subjects will be required to bring the completed dosing diary and all empty and unused study drug ampoules to each scheduled study visit. At each visit, all study drug returned by the subject (used and unused) will be collected and new study drug will be dispensed. The appropriate study personnel must document the number of used and unused ampoules and determine if the appropriate amount of study drug remains based on the dose of study drug prescribed.

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each study visit, the subject will be asked whether he or she has been compliant

with dosing instructions. If it is determined that a subject is not compliant with study drug then site personnel must re-educate the subject on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor.

7 EXPERIMENTAL PROCEDURES

Screening may begin up to 30 days prior to first dose of study drug. Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Alternately, the Screening and Baseline assessments may be conducted in 1 visit if all assessments are performed and all entry criteria are satisfied within the 48 hours prior to randomization and first dose of study drug.

7.1 SCREENING VISIT

The recommended sequence of assessments for the Screening Visit is as follows (if not combined with the Baseline Visit [see Section 7.3 for the recommended sequence of events for the combined Screening/Baseline Visit]):

- Informed consent
- Inclusion/exclusion criteria review
  - If necessary, the following procedures may be performed during the 30 day Screening window if required to satisfy inclusion/exclusion criteria (previous medical records documenting eligibility criteria may also be used provided the previous records document subject eligibility within the protocol mandated timelines, as applicable):
    - RHC (Must be performed within 1 year prior to randomization. If a historical RHC is not available in this timeframe, a RHC may be performed during Screening so long as it is performed at least 5 days prior to randomization [Baseline (Day 1)]; a RHC cannot be combined with the Baseline Visit). Select RHC parameters will be recorded in the eCRF including: mPAP, PVR, PCWP, and vasodilator response (as applicable).
    - CT scan (must be performed within 6 months prior to randomization). A redacted copy of the CT scan used to confirm subject eligibility should be sent to the Sponsor.
    - Although not required for eligibility, the date of lung biopsy for subjects with a biopsy confirmed diagnosis of ILD will be recorded in the eCRF.
- Demographics
- PH history
- Medical history

- PE
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT, if practice 6MWT is applicable); including height, weight, RR, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature.
- Blood draws for clinical laboratory parameters
- Urine pregnancy test, for women of childbearing potential
- Practice 6MWT (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT, if applicable)
- Documentation of supplemental oxygen requirement (L/min)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Complete and submit Pre-Baseline Review Form to the Sponsor for Medical Monitor review prior to randomization

7.2 BASELINE/RANDOMIZATION VISIT

All Baseline assessments must be performed prior to the first dose of study drug. Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of assessments; however, the Baseline 6MWT must occur prior to randomization. The recommended sequence of assessments for the Baseline Visit is as follows (if not combined with the Screening Visit [see Section 7.3 for the recommended sequence of events for the combined Screening/Baseline Visit]):

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- 12-lead ECG (following at least 5 minutes of rest in the semi-recumbent position)

- Documentation of supplemental oxygen requirement (L/min)
- 6MWT (must be conducted prior to randomization; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to randomization and after recovery from the Baseline 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least 1 hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation

7.3 COMBINED SCREENING AND BASELINE

The Screening and Baseline assessments may be conducted in 1 visit if all assessments are performed and all entry criteria are satisfied within 48 hours prior to randomization and dosing of study drug. Baseline PFTs, 6MWT, and CT (if a historical assessment is not available within 6 months prior to randomization) assessments used to determine eligibility criteria may be performed on the same day but prior to randomization. The recommended order of assessments for a combined Screening and Baseline Visit is outlined below.

<u>Assessments to be completed as part of the Screening Visit</u>:

- Informed consent
- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Inclusion/exclusion criteria review

  - RHC (Must be performed within 1 year prior to randomization. If a historical RHC is not available in this timeframe, a RHC may be performed during Screening so long as it is performed at least 5 days prior to randomization [Baseline (Day 1)]; a RHC cannot be combined with the Baseline Visit). Select RHC parameters will be recorded in the eCRF including: mPAP, PVR, and PCWP, and vasodilator response (as applicable).
  - CT scan (must be performed within 6 months prior to randomization). A redacted copy of the CT scan used to confirm subject eligibility should be sent to the Sponsor.
  - Although not required for eligibility, the date of lung biopsy for subjects with a biopsy confirmed diagnosis of ILD will be recorded in the eCRF.
- Blood draws for clinical laboratory parameters (enough blood should be drawn for local laboratory to confirm the entry criteria for hemoglobin, as well as for the complete panel for central laboratory processing)
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- Demographics
- PH history
- Medical history
- PE
- Vital signs (following at least 5 minutes of rest; collected prior to the 6MWT or after recovery from the 6MWT); including height, weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Practice 6MWT to be conducted 1 day prior to Baseline assessments (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Complete and submit the Pre-Baseline Review Form to the Sponsor for Medical Monitor review prior to randomization

Assessments to be completed as part of the Baseline Visit:

- Urine pregnancy test, for women of childbearing potential
- 12-Lead ECG (following at least 5 minutes of rest in the semi-recumbent position)
- 6MWT (must be conducted prior to randomization; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to randomization and after recovery from the Baseline 6MWT).
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least 1 hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation

7.4 TREATMENT PHASE: WEEKS 4, 8, AND 12

The following assessments to be completed during the Treatment Phase:

- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters (Week 8 only)
- NT-proBNP (must be drawn prior to 6MWT; for central laboratory processing only [Week 8 only])
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (Week 8 only; to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease

- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart.
  - Death (all causes)
  - Lung transplantation
- AEs
- Concomitant medications
- Dosing instructions/study drug accountability

Please note the visit window for the Week 4, Week 8, and Week 12 Visits is ± 5 days.

7.5 TREATMENT PHASE: WEEK 15 (TROUGH)

- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Urine pregnancy test, for women of childbearing potential
- Trough 6MWT (at least 4 hours after the last dose of study drug)
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation
- AEs
- Concomitant medications
- Dosing instructions/study drug accountability

Please note the visit window for the Week 15 Visit is ± 5 days and at least 24 hours prior to the Week 16 6MWT. If a subject discontinues study drug prematurely, the subject does not need to return to the clinic for the Week 15 Visit.

7.6 END OF STUDY (WEEK 16) AND/OR EARLY TERMINATION VISIT

The assessments to be completed during the Week 16 Visit are listed below in the recommended sequence of events. If a decision is made to early terminate a subject from study drug or from the study in its entirety, the following assessments should be conducted as soon as possible and prior to study drug discontinuation, if possible. If the subject permanently discontinues study drug prior to Week 16 for any reason, the subject should be encouraged to remain in the study and complete all visits (excluding the Week 15 Visit) up to and including Week 16:

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- PE
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- 12-Lead ECG (following at least 5 minutes of rest in the semi-recumbent position)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation
- AEs
- Concomitant medications
- Study drug accountability

Subjects who remain on study drug, complete all assessments during the 16-week Treatment Phase, and meet all eligibility criteria for the open-label extension study (RIN-PH-202) are eligible for an open-label extension study (RIN-PH-202). Additionally, subjects who are withdrawn from study drug prior to Week 16 due to clinical worsening should continue to return to the clinic for scheduled visits (excluding the Week 15 Visit) to be eligible for the open-label study. Refer to Section 7.8 for more information regarding access to the open-label study.

7.7 STUDY CONTACTS

During the Treatment Phase, all subjects will be contacted at least once a week via telephone or email (or more often as needed) to follow-up on adherence of the correct dose titration of study drug, and to assess for AEs and concomitant medications. A copy of emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All study contacts (ie, any dosing instructions, AEs reported, and/or medication changes) with the subject will be recorded.

The weekly study contacts 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.

7.8 ACCESS TO OPEN-LABEL STUDY

Subjects who remain on study drug, complete all assessments during the 16-week Treatment Phase, and who meet all eligibility criteria for the open-label extension study (RIN-PH-202) are eligible for an open-label extension study (RIN-PH-202). Additionally, subjects who experience clinical worsening and are withdrawn from study drug prior to Week 16 should undergo premature termination assessments prior to discontinuing study drug (when possible) and complete all remaining scheduled study visits (excluding the Week 15 Visit) through Week 16 to be eligible for entry into the open-label study.

Subjects who permanently discontinue study drug during the 16-week Treatment Phase due to treatment-related AEs are not eligible for entry into the open-label study even if they complete all remaining scheduled study visits. The site personnel must never be unblinded to the treatment assignment of these subjects unless required for safety reasons.

Subjects who permanently discontinue study drug during the 16-week Treatment Phase and do not undergo premature termination assessments prior to discontinuing study drug and/or who do not complete all remaining study visits (excluding the Week 15 Visit) through the Week 16 Visit are also not eligible for entry into the open-label study. The site personnel must never be unblinded to the treatment assignment of these subjects, unless medically necessary.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

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

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

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF and complete the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues study drug prematurely due to an AE, the subject will be followed until either the Investigator determines that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 30 days if the AE extends beyond the final visit.

If a subject discontinues study drug prematurely for any reason, the subject should be encouraged to remain in the study and attend the remaining scheduled study visits (excluding the Week 15 Visit) up to and including Week 16.

8.2 LOST TO FOLLOW-UP

If a subject fails to return to clinic or respond after at least three documented attempts by the site to contact the subject by telephone or email, the Investigator should issue a written letter

by certified mail requesting the subject to contact the clinic. If no response is received, the subject will be considered lost to follow-up. The site will record the last date of contact in the eCRF as the termination date.

8.3 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.

8.4 CRITERIA FOR DISCONTINUING THE SITE

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

- The Investigator elects to discontinue the study.
- The Sponsor elects to discontinue the study at the site.
- United States FDA, European, or national regulations are not observed.
- The protocol is consistently violated.
- Changes in personnel or facilities adversely affect performance of the study.

9 ADVERSE EVENT REPORTING

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

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product 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 medicinal product, whether or not related to the use of the medicinal product.

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.

- A 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 frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by 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).
- The disease or disorder being studied or a sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.

9.1.2 Serious Adverse Event

A SAE is an AE occurring at any time after informed consent that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Results in a medically important event of 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 serious reactions, 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the eCRF (see Appendix 15.2 for definitions). Where possible, AEs should be recorded using standard medical terminology. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. 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.

9.3 FOLLOW-UP OF ADVERSE EVENTS

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final 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 4 weeks after completion of the final study visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with any new or additional information as appropriate.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the Sponsor by fax/email [redacted]) within 24 hours of awareness.

A completed SAE Notification Report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corporation. A follow-up SAE Notification Report form must be forwarded to Global Drug

Safety at United Therapeutics Corporation within 24 hours of the receipt of any new or 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.

9.5 PREGNANCY

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via fax or email to Global Drug Safety at United Therapeutics Corporation [redacted] The United Therapeutics Global Drug Safety department will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification Form. 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.

9.6 SAFETY REPORTS

In accordance with national regulations, the Sponsor will notify the appropriate regulatory authority(ies), and all participating Investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF 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 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 screens are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify his/her 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 site after the Investigator initially signs the eCRF. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

10.3 ANALYSIS PLAN

Details of the efficacy and safety analyses are provided below. A separate statistical analysis plan will document further details of the statistical methods to be employed, including any changes to planned analyses specified within this protocol. The analysis plan will be finalized prior to any unblinding of study data by the Sponsor. Unless otherwise specified, all statistical tests will be 2-sided at alpha level of 0.05. All statistical calculations will be completed using the latest version of SAS®.

The Intent-to-Treat (ITT) population will be defined as all subjects randomized into the study and receive at least 1 dose of study drug; all ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were actually given. All efficacy analyses will be performed on this ITT population, unless otherwise specified. The Safety population will be defined as all subjects enrolled into the study who received at least 1 dose of study drug; all Safety population subjects will be counted in the group corresponding to the study drug actually received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

10.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects

with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between 2 treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.

10.3.2 Secondary Efficacy Endpoints

The effect of inhaled treprostinil will be formally tested on the following 3 secondary efficacy endpoints:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of NT-proBNP from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

The similar approach for the analysis of primary efficacy endpoint will be used. No adjustment for multiplicity is planned.

10.3.3 Exploratory Endpoints

The effect of inhaled treprostinil will be evaluated on the following parameters:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD at from Baseline to Week 8
3. Change in SGRQ from Baseline to Week 16
4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
    a. Hospitalization due to a cardiopulmonary indication
    b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
    c. Death (all causes)
    d. Lung transplantation
5. Change in DSP from Baseline to Week 16
6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16
7. Optional evaluation of whole genome sequence at Baseline

For changes in peak 6MWD and SGRQ, a similar approach for the analysis of primary efficacy endpoint will be used. For time to clinical worsening, Kaplan-Meier estimator will be provided and log-rank test will be used to compare the treatment difference.

10.3.4 Safety Analyses

The safety of inhaled treprostinil will be evaluated by comparison of the following parameters between the 2 treatment groups:

1. AEs
2. Oxygenation
   a. Pulse oximetry (SpO_2)
   b. Supplemental oxygen (L/min) requirement
3. Pulmonary function:
   a. FEV1
   b. FVC
   c. TLC
   d. DLCO
4. Clinical laboratory parameters
5. Vital signs
6. 12-Lead ECG
7. Hospitalization due to cardiopulmonary indications
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

All AEs as recorded by the Investigators will be assigned a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class by the Sponsor for reporting purposes. The summary of AEs will include the number and percentage of subjects, as well as the number of events reported for each preferred term. No inferential analyses are planned for the AEs.

Data collected prior to dosing will serve as Baseline values for the evaluation of data collected during the Treatment Phase. Summary statistics will be calculated for measured values and changes from Baseline values. Treatment-emergent changes in vital signs, ECGs, PFTs, oxygenation parameters, and clinical laboratory parameters will be summarized by treatment group. Incidence of hospitalization due to cardiopulmonary indications and exacerbations of underlying lung disease will be summarized by treatment group. No inferential analyses are planned on these safety endpoints.

10.4 INTERIM ANALYSES

Interim analyses for safety data will be performed at the request of the Data Monitoring Committee (DMC). Interim analyses for efficacy data are not planned for this study.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the clinical study report.

10.7 DATA MONITORING COMMITTEE

A DMC will be established for the study including physicians knowledgeable in the treatment of PH. Throughout the course of the study the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DMC charter. The DMC will be blinded to individual subject treatment allocation during the review process. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The Sponsor will only have access to blinded study data during this process.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

11.1.1 Study Drug

The Sponsor will supply study medication (treprostinil inhalation solution, 0.6 mg/mL or placebo), as clear liquid in 2.9 mL ampoules. The ampoules will be packaged in groups of 4, sealed in aluminum pouches. There will be 9 pouches per carton.

11.1.2 Study Device

The Sponsor will supply commercially available TD-100 nebulizers (Tyvaso Inhalation System) and accessories to the site in standard packaging labeled with the study number. The Tyvaso Inhalation System will also be provided with the commercially available IFU.

Each subject will receive 2 nebulizers at the start of the study. In addition, the subjects will be provided with a month worth of plastic accessories at each study visit.

11.2 LABELING

11.2.1 Study Drug

The foil pouch and the outer carton will each be labeled with the same information and sent to the site. At a minimum, the study medication outer packaging (pouch and carton) will be labeled to disclose clearly the product name, study number, kit identification number, expiry date, Sponsor's name and address, IFU, and storage information (subject to regulatory requirements in each study region or country).

11.2.2 Study Device

Study subjects will receive commercially available TD-100 nebulizers and accessories separately from study drug. Study subjects will receive 2 devices at Baseline supplied as a device starter kit. Subjects will receive replacement parts as part of a monthly device resupply kit. The nebulizers and accessories will be supplied using standard packaging labeled with the study number.

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. Keep the ampoules in the foil pouch to protect from light. Once the foil pouch is opened, use within 7 days. See investigational medicinal product label for information on use and storage of the product.

Study drug 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 subject not participating in this protocol.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At Baseline, an IXRS will be utilized to randomize the subjects and assign the appropriate study drug for the first 4-week treatment interval. At subsequent study visits, the IXRS will be utilized by study staff to assign subsequent study drug kits to the subjects based

upon their current treatment allocation. At each study visit, all study drug dispensed to a subject should be returned to the study site, including all used and unused ampoules.

At the end of the study, nebulizers used during the study should be collected from each subject not continuing into the open-label extension study. Subjects continuing into the open-label extension study will retain their devices for use in the open-label extension study.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records include, but are not limited to: the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of used/unused study drug returned to the site from the subject.

At each visit, site personnel will:

- Collect and document all study drug returned by the subject (both used and unused).
- Compute study drug compliance using the dosing instructions given to the subject since the previous study visit and the amount of study drug returned.
- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

Once a representative from the Sponsor is able to confirm drug accountability for a completed subject, study drug will be returned to a Sponsor designated location for destruction and/or destroyed onsite per institutional policy. At the end of the study, nebulizers used during the study should be collected from each subject not continuing into the open-label extension study. These nebulizers will be returned to a Sponsor designated location for destruction. In the event of device malfunction, at any point during the study, the nebulizer should be returned to the Sponsor. Subjects continuing into the open-label extension study will retain their devices for use in the open-label extension study.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and all applicable national regulations.

The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to those regulatory authorities and IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/EC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/EC-approved ICF prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject and the original will be retained in the study site's records.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/EC and provide the Sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's ICF and any other written information provided to the subject 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/EC's 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, at a minimum, the following documents will be provided to the site: Investigator's Brochure, Protocol, ICF, Subject Dosing Diary, the Tyvaso Inhalation System IFU, Clinical Trial Agreement, Budget Agreement, and eCRF.

At a minimum, the site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/EC Composition and Roster, IRB/EC protocol and informed consent approval letters, and Curriculum Vitae of study staff listed on the Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, the FDA or other regulatory bodies, and the IRB/EC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/EC or the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects and any report published will not identify the subject's name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

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

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

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

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

13.2 STUDY DOCUMENTATION AND STORAGE

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

13.3 STUDY MONITORING AND DATA COLLECTION

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

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

14 REFERENCES

Agarwal M, Waxman AB. Inhaled treprostinil in group-3 pulmonary hypertension. J Heart Lung Transplant. 2015;34(4):S343.

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.

Bajwa A, Shujaat A, Thomas C, et al. The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Pulm Circ. 2016. Epub ahead of print.

Benza RL, Seeger W, McLaughlin VV, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study open-label extension. J Heart Lung Transplant. 2011;30(12):1327-1333.

Channick RN, Olschewski H, Seeger W, et al. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. J Am Coll of Cardiol. 2006;48(7):1433-1437.

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. Am J Respir Crit Care Med. 2016;194(3):265-275.

Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J. 2010;35(1):105-111.

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;129(5):1313-1321.

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.

Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest. 2012;141(1):222-231.

Lettieri CJ, Nathan SD, Browning RF, et al. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100(10):1734-1741.

McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010;55(18):1915-1922.

Nathan SD. Pulmonary hypertension in interstitial lung disease. Int J Clin Pract. 2008;62(Suppl 160):21-28.

Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. Clin Chest Med. 2013;34(4):695-705.

Remodulin (treprostinil) Injection Package Insert. United Therapeutics Corp.:Research Triangle Park, NC; December 2014.

Roccia F, Campolo B, Gallelli L, et al. Effects of ambrisentan in a patient affected by combined pulmonary fibrosis and emphysema and by severe pulmonary hypertension: clinical, functional, and biomolecular findings. Clin Drug Investig. 2013;33(6):451-457.

Saggar R, Khanna D, Vaidya A, et al. Changes in right heart hemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. Thorax. 2014;69(2):123-129.

Seeger W, Adir Y, Barbera JA, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013;62(25 Suppl): D109-116.

Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S43-54.

Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-748.

Voswinckel R, Ghofrani HA, Grimminger F, et al. Inhaled treprostinil [corrected] for treatment of chronic pulmonary arterial hypertension. Ann Intern Med. 2006;144(2):149-150.

Wang L, Bai L, Sapkota R, et al. Hemodynamic and gas exchange effects of iloprost in patients with chronic obstructive pulmonary disease and pulmonary hypertension. The PVRI 8th Annual World Congress on Pulmonary Vascular Disease. The 7th Annual National Congress on Pulmonary Embolism and Pulmonary Vascular Diseases. January 14-18, 2015. Guangzhou, China.

15 APPENDICES

15.1 PROCEDURE FOR 6-MINUTE WALK TEST

General Procedures

The 6MWT should be administered by the same tester at each study site throughout the study, whenever possible. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines[1,2] and the usual practice of the investigative site. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments.

The area used for the 6MWT should be pre-measured at approximately 30 meters in length and at least 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

[1] ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002; 166: 111 117.
[2] Holland, A. E., M. A. Spruit, T. Troosters, M. A. Puhan, V. Pepin, D. Saey, M. C. McCormack, B. W. Carlin, F. C. Sciurba, F. Pitta, J. Wanger, N. MacIntyre, D. A. Kaminsky, B. H. Culver, S. M. Revill, N. A. Hernandes, V. Andrianopoulos, C. A. Camillo, K. E. Mitchell, A. L. Lee, C. J. Hill and S. J. Singh (2014). "An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease." Eur Respir J 44(6): 1428-1446.

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 minute 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.

15.2 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

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

"How are you doing (feeling)?"

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

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

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

Using provided definitions, the Investigator will then:
(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

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

INTENSITY

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

SERIOUSNESS

A serious AE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization*, is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition).

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

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (eg, hospitalization for a routine RHC).
- Treatment which was elective or 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 Decreased The dose or regimen of study drug was decreased
- 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.

15.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:

- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.