An Open-Label Extension study of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

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Protocol RIN-PH-202

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "An Open-Label Extension study of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease," protocol amendment 1 dated 18 August 2016 and agree to abide by all provisions set forth therein.

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

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

I also have read the current Clinical Investigators' Brochure for inhaled treprostinil and acknowledge that review of the information contained in the Clinical Investigators' Brochure is a requirement for Investigators before using inhaled treprostinil in a clinical trial.

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	An Open-Label Extension study 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 provide or continue to provide inhaled treprostinil for eligible subjects who participated in the RIN-PH-201 study
Secondary Objectives	To evaluate the long-term safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE
Efficacy Endpoints	1. Peak six-minute walk distance (6MWD) 2. N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) 3. Quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) 4. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 48 (or study discontinuation if prior to Week 48) 5. Change in distance saturation product (DSP)
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 one second (FEV_1)

	b. Forced vital capacity (FVC) c. Total lung capacity (TLC) d. Lung diffusion capacity (DLCO) 4. Clinical laboratory parameters 5. Vital signs 6. Hospitalizations due to a cardiopulmonary indication 7. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Study Design	Multi-center, open-label study for eligible subjects who participated in RIN-PH-201.
Sample Size	Approximately 266 subjects who completed protocol RIN-PH-201
Summary of Subject Eligibility Criteria	Inclusion criteria: 1. Subject voluntarily gives informed consent to participate in the study. 2. The subject participated in study RIN-PH-201 and: a. remained on study drug and completed all scheduled study visits or b. permanently discontinued study drug during the RIN-PH-201 study due to clinical worsening and completed all remaining required scheduled study visits or c. was enrolled in study RIN-PH-201 at the time that the study/study subject was discontinued by the sponsor. 3. Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at Baseline) and non-lactating, and will: a. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or

	b. Use two medically acceptable, highly-effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug. 4. Males must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug. Exclusion criteria: 1. The subject is pregnant or lactating. 2. The subject was prematurely discontinued from study RIN-PH-201 due to treatment related AEs. 3. The subject was prematurely discontinued from study RIN-PH-201 due to clinical worsening and did not undergo premature termination assessments prior to discontinuing study drug and/or did not complete all remaining study visits through the final scheduled visit. 4. The subject developed a concurrent illness or condition during the conduct of RIN-PH-201 which, in the opinion of the Investigator, would represent a risk to overall health if they enrolled in this study.
Drug Dosage and Formulation	Inhaled treprostinil (6 mcg/breath) Treatment phase: All subjects will initiate inhaled treprostinil at a dose of 3 breaths (18 mcg) four times daily (during waking hours). Study drug doses should be maximized throughout the study, dose escalations (additional one breath four times daily) can occur up to every three days with a maximum dosing regimen of up to 15 breaths (90 mcg) four times daily, as clinically tolerated.
Control Group	None
Route of Administration	Inhaled

Procedures	Subjects will be assessed at Baseline, Week 4, Week 12, and every 12 weeks thereafter through Week 108. Study visits will continue until each subject reaches Week 108 or until inhaled treprostinil become commercially available for patients with pre-capillary PH associated with ILD (whichever is sooner). Key Assessments: • Blood for NT-ProBNP will be obtained at Baseline, Week 48, and Week 108/study termination. • Blood for clinical labs will be obtained at all scheduled study visits. • A peak six minute walk test (6MWT) will be conducted at all scheduled study visits. • Pulse oximetry will be performed immediately prior to, during, and immediately after each scheduled 6MWT. • Pulmonary function tests (PFTs) will be conducted at Baseline, Week 12, Week 48, and Week 108/study termination. • SGRQ will be conducted at Baseline, Week 48, and Week 108/study termination. • Hospitalizations due to cardiopulmonary indications and exacerbations of underlying lung disease will be evaluated from the time of informed consent until study discontinuation. • An optional blood sample will be collected for the analysis of biomarkers (specific targets to be determined) at Baseline and Week 48 (or study termination if prior to Week 48).
Statistical Considerations	All data will be summarized in tables and listings.
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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. 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. 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 (Nathan 2008, Nathan 2013).

Combined pulmonary fibrosis and emphysema 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 pulmonary vascular resistance (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, 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 and Israel for the treatment of PAH (WHO Group I) 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 two-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 Clinical Investigators 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 six-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 four 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 findings, chest x-rays, pulmonary function tests, 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 one to

12 breaths (6 to 72 mcg) four 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 quality of life (QOL). Survival was robust with one and two year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the trial. 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 six subjects (3%) discontinued inhaled treprostinil due to cough, including one 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 I 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 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 nine COPD subjects with PH which

reported no notable changes in arterial blood gases over the 16-Week treatment period (Bajwa submitted). Finally, Agarwal and colleagues (Agarwal 2015) recently presented data on 35 patients with WHO Group 3 PH who received treatment with inhaled treprostinil for six 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 open-label study will evaluate the safety of continued therapy with inhaled treprostinil in subjects who have completed RIN-PH-201. This study hypothesizes that long-term safety findings will be similar to those observed in the randomized, placebo controlled study (RIN-PH-201).

2 OBJECTIVES

The primary objective of this study is to provide or continue to provide inhaled treprostinil for eligible subjects who participated in the RIN-PH-201 study.

Secondary objectives are to assess the long-term safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE.

2.1 EFFICACY ENDPOINTS

To evaluate the effect of continued long-term therapy with inhaled treprostinil on the following:

1. Peak 6MWD
2. N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)
3. Quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)
4. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 48 (or study discontinuation if prior to Week 48)
5. Change in distance saturation product (DSP)

2.2 SAFETY ENDPOINTS

To evaluate the effect of continued long-term therapy with inhaled treprostinil on the following:

1. Adverse events (AEs)
2. Oxygenation
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2])
   b. Supplemental oxygen (L/min) requirement
3. Pulmonary function:
   a. Forced expiratory volume in one second (FEV_1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Hospitalizations due to a cardiopulmonary indication
7. 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 multi-center, open-label study. Study visits will occur at Baseline, Weeks 4, 12, and every 12 weeks thereafter until Week 108. The study will continue until each subject has completed Week 108 or until inhaled treprostinil become commercially available for patients with pre-capillary PH associated with ILD including CPFE (whichever is sooner).

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

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Study Procedures	**Baseline[1]**	**Treatment Phase**			
Study Week		**Week 4[2]**	**Week 12[2]**	**Follow-up Visits (every 12 weeks through study termination)[2]**	**Week 108 / Study Termination Visit**
Informed Consent[1]	X				
Subject Eligibility[1]	X				
SGRQ[1]	X			X[13]	X
Physical Examination[1]	X				X
Vital Signs[1,3]	X	X	X	X	X
Clinical Laboratory Assessments[1]	X	X	X	X	X
N-terminal proBNP[1,4]	X			X[13]	X
Blood sample for biomarker evaluation (optional)[5]	X			X[13]	X[13]
Urine Pregnancy Test[1,6]	X	X	X	X	X
Peak 6MWT[1,7]	X	X	X	X	X
Pulse Oximetry[1,8]	X	X	X	X	X
Documentation of Supplemental Oxygen Requirement	X	X	X	X	X
PFTs[1,9]	X		X	X[13]	X
Dosing instructions / Dosing / Accountability	X	X	X	X	X
Telephone/Email Contact[10]		X	X	X	
Adverse Events[11,12]	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Hospitalizations[14]	X	X	X	X	X
Exacerbations of Underlying Lung Disease[15]	X	X	X	X	X

NT-ProBNP: N-terminal brain natriuretic peptide; PFTs: pulmonary function tests; PH: pulmonary hypertension; SGRQ: St. George Respiratory Questionnaire; 6MWT: six-minute walk test

[1] Baseline assessments (6MWT, pulse oximetry, PFTs, SGRQ, clinical laboratory assessments, NT-ProBNP, urine pregnancy test, optional biomarker sample [as applicable], vitals, and physical examination) for this study are those collected at the Study Termination Visit (Week 16) from study RIN-PH-201 and prior to initiation of open-label study drug. Informed consent and subject eligibility criteria are exclusive to this protocol.

[2] The visit window for the Week 4 visit is ± 5 days; the visit window for all other visits is ± 14 days. Visits are scheduled based off of the day of first dose of study drug for the RIN-PH-202 study (i.e., four weeks after the first dose of study drug in this open-label study).

[3] Vital signs must be collected after five minutes of rest (seated); no other measurements or procedures should be performed during this five minute period. When applicable, 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. Vital signs measured will include blood pressure (systolic and diastolic), heart rate (HR), respiratory rate (RR), temperature, and weight.

[4] Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT at Week 48 and Study Termination.

[5] For subjects consenting to the optional biomarker sample. The optional biomarker sample must be drawn prior to conducting the 6MWT at Week 48 only or upon early termination if subjects discontinue the study prior to Week 48.

[6] For females of childbearing potential.

[7] The 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.

[8] Pulse oximetry will be performed immediately prior to, during, and immediately after 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 (and corresponding HR) obtained during each 6MWT will be recorded in the eCRF.

[9] PFTs will include the evaluation of FEV_1, FVC, TLC, and DLCO. PFTs should be performed after recovering from the 6MWT.

[10] Telephone contact should occur at least weekly for the first 12 weeks of the study and at least monthly thereafter. Telephone 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. 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.

[11] Any AEs that are ongoing at the Study Termination Visit from study RIN-PH-201 should be recorded as continuing AEs in this open-label study.

[12] Any AEs that are ongoing at the Study Termination Visit for this protocol (RIN-PH-202) should be followed for up to 30 days after completion of the Study Termination Visit.

[13] During the follow-up assessments (scheduled every 12 weeks after Week 12), the SRGQ, PFTs, and NT-pre-BNP are only required at Week 48 and Week 108/Study Termination. For those subjects consenting to the optional biomarker sample, this sample is only required at Week 48 (or upon early termination if prior to Week 48).

[14] 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.

[15] Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Exacerbations will also be recorded as AEs.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 Six-Minute Walk Test (6MWT)

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 peak 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. The peak 6MWT must be conducted between 10 to 60 minutes after the most recent dose of study drug.

A peak 6MWT will be conducted at Baseline as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201. A peak 6MWT will also be performed at Week 4, Week 12, every 12 weeks thereafter, and at Week 108/Study Termination.

3.3.1.2 St. George's Respiratory Questionnaire

The SGRQ will be conducted at Baseline as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201. The SGRQ will also be conducted at Week 48 and at Week 108/Study Termination. The SGRQ should be completed as the first assessment during these visits 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 (NT-proBNP)

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 as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201. NT-proBNP will also be collected at Week 48 and at Week 108/Study Termination. Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT.

3.3.1.4 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 as part of the Study

Termination (Week 16) assessments from protocol RIN-PH-201 and at Week 48 (or upon early termination if prior to Week 48).

3.3.1.5 Change in DSP

Change in DSP is the product of distance walked and lowest oxygen saturation 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 in DSP will be calculated from Baseline to Week 4, Week 12, every 12 weeks thereafter, and at Week 108/Study Termination.

3.3.2 Safety

During this study, treatment emergent changes in physical examination (PE) findings, vital signs, clinical laboratory parameters, PFTs, oxygenation, hospitalizations due to a cardiopulmonary indication, exacerbations of underlying lung disease, and the development of AEs after treatment will be the primary assessments of safety.

3.3.2.1 Physical Examinations

A complete physical examination (PE) will be conducted during Baseline as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201. A follow-up PE will also be performed at the Study Termination Visit. Any clinically significant changes from Baseline noted during the course of the study or during the Study Termination PE should be reported as AEs.

3.3.2.2 Vital Signs

Vital signs will be assessed at Baseline as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201 and at each subsequent study visit and at the Study Termination Visit. Vital signs measured will include blood pressure (systolic and diastolic), heart rate (HR), respiratory rate (RR), temperature, and weight. Vital signs must be assessed following at least five minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures should be performed during this five-minute period. When applicable, 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 from the 6MWT. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms.

3.3.2.3 Clinical Laboratory Assessments

Clinical laboratory parameters will be assessed at Baseline as part of Study Termination assessments from protocol RIN-PH-201. Clinical laboratory assessments will also be assessed at Week 4, Week 12, at every scheduled Follow-up Visit thereafter, and at the Week 108/Study Termination Visit. Clinical laboratory parameters to be assessed at the study visits are listed below:

Electrolyte Panel	Chemistry Panel	Hematology Panel
• Sodium	• Total bilirubin	• Hemoglobin
• Potassium	• Alkaline phosphatase	• Hematocrit
• Bicarbonate	• Alanine aminotransferase	• Red blood cell count
• Chloride	• Aspartate aminotransferase	• Red blood cell morphology
	• Urea nitrogen	• White blood cell count
	• Creatinine	• Platelet count
	• Calcium	
	• Albumin	

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.

A urine pregnancy test will be collected at every visit for females of childbearing potential. 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.

3.3.2.4 Pulmonary Function Tests (PFTs)

Pulmonary Function Tests (PFTs) will be assessed at Baseline as part of the Study Termination (Week 16) assessments from protocol RIN-PH-201 and at Week 12, Week 48, and at Week 108/Study Termination. If the PFT is done both prior to and after a

bronchodilator, only the pre-bronchodilator values will be recorded. Pulmonary function tests should be conducted after recovery from the 6MWT.

The following parameters will be recorded (absolute values and % predicted): FEV_1, FVC, TLC, and DLCO (uncorrected for hemoglobin and lung volume).

3.3.2.5 Oxygenation

3.3.2.5.1 Pulse Oximetry

Pulse oximetry will be assessed immediately prior to, throughout the conduct of, and immediately after each scheduled 6MWT assessment at Baseline (as part of the RIN-PH-201 Study Termination Visit), Week 4, Week 12, every 12 weeks thereafter, and at Study Termination. 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 with the associated HR 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 (i.e., 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.

3.3.2.5.2 Supplemental Oxygen Requirement

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

3.3.2.6 Adverse Events

Any AEs that are ongoing at the Study Termination Visit for the RIN-PH-201 study should be recorded as continuing AEs in this open-label study.

Adverse events will be recorded throughout the course of the study from the time that each subject signs the ICF until the subject is either discontinued from the study or all Study Termination 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 (*i.e.,* 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 (Study Termination). All AEs/SAEs that occur while the subject is on study drug will be recorded as instructed in this protocol.

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

3.3.2.7 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. Concomitant medications that were ongoing at the end of the RIN-PH-201 study will be recorded in the eCRF for the open-label study.

3.3.2.8 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.

3.3.2.9 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 one month duration
3. 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 four 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.

3.3.2.10 Telephone/Email Contact

Weekly telephone/email contact is required for the first 12 weeks of the study to instruct the subject to titrate their dose of study drug and to assess for AEs and concomitant medications. After the first 12 weeks, telephone/email contact must occur at least monthly.
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 (*i.e.*, any dosing instructions, AEs reported and/or medication changes) with the subject must be noted in the source documentation.

3.3.2.11 Continued Access Plan

Subjects who have completed the Week 108/Study Termination Visit will be given the option for continued access to inhaled treprostinil. During Week 108/Study Termination Visit, the Investigator should assess each subject's eligibility for the Continued Access Plan.

3.4 NUMBER OF SUBJECTS

Approximately 266 subjects who completed protocol RIN-PH-201.

3.5 NUMBER OF CENTERS

This study is a multi-center with approximately 100 participating study centers. Only those centers who participated in the RIN-PH-201 study will take part in this study.

3.6 ESTIMATED STUDY DURATION

The study will continue until each subject reaches Week 108 or until inhaled treprostinil become commercially available for patients with pre-capillary PH associated with ILD (whichever is sooner).

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 open-label 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. The subject participated in study RIN-PH-201 and:
    a. remained on study drug and completed all scheduled study visits or
    b. permanently discontinued study drug during the RIN-PH-201 study due to clinical worsening and completed all remaining required scheduled study visits or
    c. was enrolled in study RIN-PH-201 at the time that the study/study subject was discontinued by the sponsor.
3. Females of reproductive potential[1] must be non-pregnant (as confirmed by a urine pregnancy test at Baseline) and non-lactating, and will:
    a. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
    b. Use two medically acceptable, highly-effective forms of contraception[2] for the duration of study, and at least 30 days after discontinuing study drug.
4. Males must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.

[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.

4.2 EXCLUSION CRITERIA

1. The subject is pregnant or lactating.
2. The subject was prematurely discontinued from study RIN-PH-201 due to treatment related AEs.
3. The subject was prematurely discontinued from study RIN-PH-201 due to clinical worsening and did not undergo premature termination assessments prior to discontinuing study drug and/or did not complete all remaining study visits through the final scheduled visit.
4. The subject developed a concurrent illness or condition during the conduct of RIN-PH-201 which, in the opinion of the Investigator, would represent a risk to overall health if they enrolled in this study.

4.3 PRESCRIBED THERAPY

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

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 3.3.2.5.2.

Subjects who initiate pulmonary rehabilitation during the course of the study should also record this information in the eCRF.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

All subjects will receive inhaled treprostinil during this open-label study. Subjects will retain the same subject number as assigned for the RIN-PH-201 study.

5.2 RANDOMIZATION

This study is not randomized.

5.3 BLINDING

This study is not blinded.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. All subjects will receive study drug (inhaled treprostinil) 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.

All subjects will initiate study therapy at 3 breaths (18 mcg) regardless of treatment assignment or dose in the randomized study. Open-label study drug will be initiated after study drug is discontinued from the RIN-PH-201 (blinded study) and after the subject has signed informed consent and enrolled into the open-label study. Study drug doses should be maximized throughout the study, dose escalations (additional one breath four times daily) can occur up to every three days with a maximum dosing regimen of up to 15 breaths (90 mcg) four times daily, as clinically tolerated. Table 6-1 provides a guideline for recommended dose escalations.

Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table

Study Day[1]	Single Dose	Total Daily Dose
Titrating to maximum dose of up to 15 breaths as clinically tolerated		
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
28-30	12 breaths QID (72 mcg)	288 mcg
31 (and beyond)	Up to 15 breaths QID (90 mcg)	360 mcg

* QID: four times daily; mcg: micrograms

[1] 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. More frequent dose titrations may be considered at the discretion of the treating physician.

If subjects are unable to tolerate the initial three breaths, they may decrease their next dose to one or two breaths of study drug (as determined by the Investigator) four times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of three breaths and titrate to up to a maximum of 15 breaths four times a day during waking hours.

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 for the first 12 weeks (and monthly thereafter) to monitor for AEs and make decisions about dose titration.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

This study is not blinded.

6.3 COMPLIANCE

Subjects will be required to bring all empty study drug ampoules to each scheduled study visit. Starting at Week 12, all study drug returned by the subject (used and unused) will be collected and new study drug will be dispensed. Study drug will not be supplied at the Week 4 visit unless required for emergency purposes (*i.e.*, to replace lost study drug, etc.); however, the subject should still return empty drug ampules for drug accountability purposes. 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.

Subjects may use a dosing diary to track dosing during the open-label study at discretion of the investigator/subject.

7 EXPERIMENTAL PROCEDURES

7.1 BASELINE

All data collected at the subject's Study Termination Visit (Week 16) during RIN-PH-201 and prior to initiating open-label study drug will serve as Baseline assessments for this study. Subjects must sign an informed consent form and meet inclusion/exclusion criteria specific to this protocol. The recommended sequence of events for Baseline is displayed below:

- Informed consent (prior to any study assessments)
- Inclusion/exclusion criteria
- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)*
- Physical examination*
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT)*
- Urine pregnancy test, for women of childbearing potential*
- Blood draws for clinical laboratory parameters*
- NT-proBNP (must be drawn prior to 6MWT)*
- 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 and throughout the conduct of the 6MWT)*
- Documentation of supplemental oxygenation requirement (L/min)
- PFTs (to be performed after recovery from the 6MWT)*
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications*
- Study drug administration (all subjects will be initiated on inhaled treprostinil at a dose of 3 breaths four times daily during waking hours).

*Assessments conducted during the Study Termination Visit (Week 16) for the RIN-PH-201 study will not need to be repeated.

Adverse events that were ongoing at the end of the RIN-PH-201 study will be recorded as ongoing events for this open-label study. Concomitant medications that were ongoing at the RIN-PH-201 Study Termination Visit will be recorded in the eCRF for the open-label study. Once the subject signs the informed consent form for this study, all AEs must be recorded and documented in the eCRF for this study until the time of study discontinuation. Telephone calls/email to the subject must begin within one week of the subject receiving the first dose of study drug and continue to be made weekly for the first 12 weeks of the study. After the first 12 weeks, phone calls must be made at least monthly. Dose titration should occur as outlined in Section 6.1.

7.2 TREATMENT PHASE

7.2.1 Week 4 Visit

Subjects are to return to the study site at Week 4. This visit should be conducted within ± 5 days of the scheduled visit (as determined by the first dose of open-label study drug). The recommended sequence of events for the Week 4 visit is below:

- Blood draws for clinical laboratory parameters
- Urine pregnancy test, for women of childbearing potential
- Vital signs (following at least five minutes of rest)
- 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)
- Documentation of supplemental oxygenation requirement (L/min)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications
- Study drug accountability (Study drug will be returned but not be supplied at the Week 4 visit unless required for emergency purposes [i.e., to replace lost study drug, etc.]).

Telephone calls/email to the subject should continue to be made weekly for the first 12 weeks of the study. After the first 12 weeks, phone calls must be made at least monthly. Dose titration should occur as needed in occurrence with Section 6.1.

7.2.2 Week 12 Visit

Subjects are to return to the study site at Week 12. This visit should be conducted within ± 14 days of the scheduled visit (as determined by the first dose of open-label study drug). The recommended sequence of events for the Week 12 visit is below:

- Blood draws for clinical laboratory parameters
- Urine pregnancy test, for women of childbearing potential
- Vital signs (following at least five minutes of rest)
- 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)
- Documentation of supplemental oxygenation requirement (L/min)
- PFTs (to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications
- Study drug accountability

Telephone calls/email to the subject should continue to be made at least monthly for the remainder of the study.

7.2.3 Follow-up Visits (every 12 weeks after Week 12 until Week 108 / Study Termination)

Subjects are to return to the study site every 12 weeks after Week 12 (as determined by the first dose of open-label study drug). These visits should be conducted within ± 14 days of the scheduled visit (as determined by the first dose of open-label study drug). The recommended sequence of events for the follow-up visits is below:

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws; **Week 48 ONLY**)*

- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT; **Week 48 ONLY**)*
- Collection of blood sample for evaluation of biomarkers (optional; **Week 48 ONLY**)
- Vital signs (following at least five minutes of rest)
- 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)
- Documentation of supplemental oxygenation requirement (L/min)
- PFTs (to be performed after recovery from the 6MWT; **Week 48 ONLY**)*
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications
- Study drug accountability

*Assessments conducted during the Week 48 visits ONLY.

Telephone calls/email to the subject should continue to be made at least monthly for the remainder of the study.

7.3 WEEK 108 / STUDY TERMINATION VISIT

The Week 108 visit will be the Study Termination Visit. In addition, if a subject discontinues the study prior to Week 108, they will complete a Study Termination Visit. If possible, each subject should remain on study drug until they have completed the Study Termination Visit. The following assessments will occur at the Study Termination Visit:

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Physical examination
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT)
- Collection of blood sample for evaluation of biomarkers (optional; only in those subjects who discontinue prior to Week 48)

- 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)
- Documentation of supplemental oxygenation requirement (L/min)
- PFTs (to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications
- Study drug accountability

7.3.1 Study Contacts

All subjects will be contacted at least once a week for the first 12 weeks and then monthly thereafter 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 (*i.e.,* 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.

7.3.2 Continued Access Plan

Subjects who have completed the Week 108/Study Termination Visit will be given the option for continued access to inhaled treprostinil (Section 3.3.2.11). During Week 108/Study Termination Visit, the Investigator should assess each subject's eligibility for the Continued Access Plan.

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.
- The subject's behavior is likely to undermine the validity of his/her results.
- The subject permanently initiates an infused prostacyclin therapy for >29 days.
- The subject becomes pregnant.

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.

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.
- U.S. Food and Drug Administration (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

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 (*e.g.,* 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 the use of the term "adverse event".

An AE does not include the following:

- Medical or surgical procedures (*e.g.,* 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 (*e.g.,* 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 serious adverse event (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 one 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 four 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.

If, at any time, the subject withdraws from the study and/or changes from study drug to commercially available Tyvaso, any AEs/SAEs that occur on Tyvaso (including product use errors, product quality problems, and therapeutic failures) will be reported following local post-marketing reporting requirements, or Continued Access Plan local reporting requirements (see Section 3.3.2.11). These events will not be included in the protocol analysis.

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 Investigational Review Board (IRB) or Ethics Committee (EC) of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

9.5 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 e-mail 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

No formal sample size calculation has been conducted. All eligible subjects from RIN-PH-201 may enter this study.

10.3 ANALYSIS PLAN

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

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

10.4 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.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

The Sponsor will supply study drug (treprostinil inhalation solution, 0.6 mg/mL), as clear liquid in 2.9 mL ampoules. The ampoules will be packaged in groups of four, sealed in aluminum pouches. There will be nine pouches per carton and each subject will receive three

cartons at Baseline, Week 12, and each scheduled follow-up visit thereafter (*i.e.*, every 12 weeks). Study drug will not be supplied at the Week 4 visit unless required for emergency purposes (*i.e.*, to replace lost study drug, etc.).

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 will also be provided with the commercially available Instructions for Use (IFU).

Each subject will continue to use the assigned nebulizers provided in the RIN-PH-201 study for this study. In addition, the subjects will be provided with three months' worth of plastic accessories at Baseline, Week 12, and each scheduled follow-up visit thereafter. Nebulizers will be replaced at least every two years (date determined based off of first use in RIN-PH-201).

11.2 LABELING

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, instructions for use, and storage information (subject to regulatory requirements in each study region or country).

Study subjects will receive commercially available TD-100 nebulizers and accessories separately from study drug. Study subjects will utilize the TD-100 nebulizers from the RIN-PH-201 study at study entry. Subjects will receive replacement parts every three months as part of 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 TRIAL MATERIAL (CTM)

All study drug will be stored at room temperature 25°C (77°F) with excursions permitted to 15°C-30°C (59°F – 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 seven 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 CTM

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 assign study drug for the first 12-week treatment interval. At subsequent study visits, the IXRS will be utilized by study staff to assign subsequent study drug kits to the subjects. Starting at Week 12 and at every scheduled study visit thereafter, all study drug dispensed to a subject should be returned to the study site, including all used and unused ampoules. Subjects may also return used ampoules at the Week 4 visit; however, unused ampules should not be returned until the Week 12 visit to ensure the subject has enough drug to get through Week 12.

At the end of the study, nebulizers used during the study should be collected from each subject.

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 [unused drug will not be collected at the Week 4 visit to ensure the subject has enough drug to get through the Week 12 visit]).
- 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).
- Review the subject dosing diary, if applicable (the use of a dosing diary is optional for this open-label study)

Once a representative from the Sponsor is able to confirm drug accountability for a completed subject, unused study drug and nebulizers will be returned to a Sponsor designated location for destruction.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 APPLICABLE REGULATORY REQUIREMENTS

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

12.2 INFORMED CONSENT REQUIREMENTS

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

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/EC and provide the sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's informed consent form and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the informed consent form and advertising materials

must be forwarded to the Sponsor for review before submission to the IRB/EC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the informed consent form, the Investigator is responsible for obtaining IRB/EC approval of these amended documents prior to implementation. Copies of the IRB/EC correspondence and approval letters must be sent to the Sponsor.

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

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

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical trial, at a minimum, the following documents will be provided to the site: Investigators' Brochure, Protocol, Informed Consent Form, Dosing Diary, the Tyvaso Inhalation System IFU, Budget Agreement, and Case Report Form.

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 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 two 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 two 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.

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15 APPENDICES

15.1 PROCEDURE FOR SIX-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.

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 should 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 (e.g., chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the six-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.

[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.

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.

<u>Definitions of Intensity, Seriousness, Causality, Action Taken, and Outcome</u>

INTENSITY

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

SERIOUSNESS

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

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

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (e.g., hospitalization for a routine RHC).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (e.g., 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
☐	☐	☐	☐	☐

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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.