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A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)

IND Number 70,362

Protocol RIN-PH-304

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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Amendment 4 Date:	20 October 2020

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)," Amendment 4, dated 20 October 2020 and agree to abide by all provisions set forth therein.

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

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

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

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title: A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)

Study Phase: 3

Indication: Inhaled treprostinil (Tyvaso®) is a prostacyclin vasodilator being studied for the treatment of pulmonary hypertension due to chronic obstructive pulmonary disease (PH-COPD; World Health Organization [WHO] Group 3) to improve exercise ability.

Primary Objective: To demonstrate the efficacy of inhaled treprostinil compared to placebo in improving exercise ability as measured by change from baseline in 6-Minute Walk Distance (6MWD) following 12 weeks of active treatment in subjects with PH-COPD.

Secondary Objective(s): To assess the effect of inhaled treprostinil compared to placebo after 12 weeks of active treatment on the following:

1. Change in moderate to vigorous physical activity (MVPA) as measured by actigraphy
2. Change in overall activity as measured by actigraphy
3. Change in Borg dyspnea score from baseline
4. Change in 6MWD/Borg dyspnea composite score from baseline
5. Change in quality of life (QOL) from baseline as measured by St. George's Respiratory Questionnaire (SGRQ) and the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)
6. Change in plasma concentration of N-Terminal pro-brain natriuretic peptide (NT-proBNP) from baseline
7. Change in patient global assessment (PGA)

Safety Objective(s): To assess the safety of inhaled treprostinil compared to placebo on the following:

1. Adverse events (AEs)
2. Clinical laboratory assessments
3. Electrocardiograms (ECGs)
4. Physical examination (PE) findings
5. Oxygenation
6. Pulmonary function tests (PFTs)
7. Vital sign measurements
8. At-home spirometry

Exploratory Objectives:	[redacted]

Study Design: This is a multicenter, randomized, double-blind, placebo-controlled, 34-week, crossover study with a Treatment Period of approximately 26 weeks under the **Original Crossover Design** or, if applicable, a 21-week parallel study with a Treatment Period of approximately 14 weeks under the **Contingent Parallel Design**.

Sample Size: Approximately 136 subjects will be randomized at approximately 80 US and international sites in the **Original Crossover Design**. If the study is adapted to the **Contingent Parallel Design**, approximately 314 subjects will be randomized at approximately 100 US and international sites.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

Subjects who meet the following criteria may be included in the study:

1. Voluntarily gives informed consent to participate in the study.
2. Males and females 18 years of age and above at the time of informed consent.
    a) Females of childbearing potential (defined as less than 1 year postmenopausal and not surgically sterile) must agree to practice abstinence or use 2 highly effective methods of contraception (defined as a method of birth control that results in a less than 1% per year failure rate, such as approved hormonal contraceptives, barrier methods [condom or diaphragm] used with a spermicide, or an intrauterine device) for the duration of study treatment and for 48 hours after discontinuing study drug. Subjects must have negative pregnancy tests at Screening Visit 1 (urine [prior to the first dose of study drug] and serum) and the Baseline Visit (urine [Study Week 1]).
    b) Males with a partner of childbearing potential must agree to use a barrier method (condom) with a spermicide for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. Diagnosis of PH-COPD (WHO Group 3).

4. Clinical diagnosis of COPD per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria (2020) and documented spirometry parameters measured during Screening Visit 1 (prior to start of low dose inhaled treprostinil), as follows:
   a) Forced expiratory volume in 1 second (FEV_1) <80% predicted
   b) FEV_1/Forced vital capacity (FVC) <70
5. Resting saturation peripheral capillary oxygenation (SpO_2) ≥90% during Screening Visit 1, with or without supplemental oxygen, and supplemental oxygen cannot exceed 10 L/min by any mode of delivery.
6. A 6MWD ≥100 meters during Screening Visit 1 (prior to start of low dose inhaled treprostinil).
7. Willing to undergo right heart catheterization (RHC) during Screening Visit 1. A RHC performed within 12 months prior to the start of Screening Visit 1 is acceptable for determining eligibility, even if done without oxygen or vasodilator challenge, and a repeat RHC is not required. The following parameters must be documented for eligibility:
   a) Pulmonary vascular resistance (PVR) ≥4 Wood units
   b) Pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) of ≤15 mmHg
   c) Pulmonary artery pressure mean (PAPm) of ≥30 mmHg
8. Must be on a stable and optimized dose of chronic COPD medications for ≥30 days prior to the start of Screening Visit 1 and remain on the same dose throughout the Screening Period.
9. Can communicate effectively with study personnel and is considered reliable, willing, and likely to be cooperative with protocol requirements, including attending all study visits, in the opinion of the Investigator.

Exclusion Criteria:

Subjects who meet the following criteria are excluded from the study:

1. A diagnosis of either pulmonary arterial hypertension (PAH) or pulmonary hypertension (PH) due to reasons other than COPD, including, but not limited to, chronic thromboembolic PH or acute/recent deep vein thrombosis or pulmonary embolism, untreated or inadequately treated obstructive sleep apnea, connective tissue disease (including, but not limited to, systemic sclerosis/scleroderma or systemic lupus erythematosus), sarcoidosis, human immunodeficiency virus-1 infection, and other conditions under WHO Group 1, 2, 4, and 5 classifications.
2. A confirmed diagnosis of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, diffuse parenchymal lung disease, or interstitial lung disease, based on chest CT imaging during Screening Visit 1. A chest CT performed within 6 months prior to the start of Screening Visit 1 is acceptable for determining eligibility and a repeat assessment is not required. A redacted CT scan report (from Screening Visit 1 or dated within 6 months prior) should be provided to the

Sponsor's Medical Monitor with the Pre-Baseline Review Form to confirm eligibility.

3. Received any Food and Drug Administration (FDA)-approved medication for the treatment of PAH (ie, prostacyclin, prostacyclin receptor agonist, endothelin receptor antagonist [ERA], phosphodiesterase type 5 inhibitor [PDE5-I], or soluble guanylate cyclase [sGC] stimulator) at Screening Visit 1 and thereafter, except if received for acute vasoreactivity testing.
4. Previous diagnosis of homozygous alpha-1 antitrypsin deficiency.
5. Any prior intolerance to inhaled prostanoid therapy.
6. Inability to tolerate low dose inhaled treprostinil and/or follow dosing regimen during the Screening Period (pre-randomization).
7. Unwilling or unable to use Sponsor-provided devices (actigraph, spirometer, or smart device).
8. Evidence of clinically significant left-sided heart disease (including, but not limited to, left ventricular ejection fraction <40%, left ventricular hypertrophy) or clinically significant cardiologic conditions, such as congestive heart failure, coronary artery disease, or valvular heart disease. NOTE: Subjects with abnormal left ventricular function attributable to the effects of right ventricular overload will not be excluded, but a discussion with and approval by the Sponsor's Medical Monitor is required.
9. Any exacerbation of COPD (including hospitalization or outpatient therapy) or active pulmonary or upper respiratory infection from 30 days prior to start of Screening Visit 1 through the Baseline Visit. This is defined as worsening of respiratory symptoms that required treatment with corticosteroids and/or antibiotics.
10. Initiation of pulmonary rehabilitation within 12 weeks prior to start of Screening Visit 1 or, in the opinion of the Investigator, pulmonary rehabilitation is likely to be needed during the Treatment Period.
11. Any form of congenital heart disease (repaired or unrepaired) other than a patent foramen ovale.
12. Any musculoskeletal disorder (ie, severe arthritis of the lower limbs which limits ambulation, recent hip or knee joint replacement, artificial leg) or any other condition that would likely be the primary limitation to ambulation.
13. Use of any other investigational drug or device within 30 days prior to the start of Screening Visit 1.
14. Any other clinically significant illness or abnormal laboratory value(s) measured during the Screening Period that, in the opinion of the Investigator, might adversely affect the interpretation of the study data or safety of the subject.

Drug Dosage and Formulation:

- Active Study Drug: Inhaled treprostinil solution (0.6 mg/mL, 6 mcg/breath), 4 times daily (QID) during waking hours.
- Placebo Study Drug: Placebo inhalation solution, QID during waking hours.

All subjects will be given low dose inhaled treprostinil during the Screening Period. After randomization, study drug will be initiated based on randomized treatment assignment and dose adjustments will be based on subject tolerability at the discretion of the Investigator. Study drug doses should be maximized to tolerability throughout the study and dose escalations (additional 1 breath QID) can occur approximately every 3 days with a target dosing regimen of 12 breaths QID or the maximum tolerated dose.

Control Group: Placebo

Route of Administration: Inhaled

Procedures: This adaptive study will be initiated as an **Original Crossover Design**. Two separate missing data checks will occur and will result in study design adjustment decisions. The following adaptation strategies will be used:

Adaptation 1:

At approximately 75% of subjects randomized, a blinded interim analysis will be performed to assess the extent of missing primary efficacy endpoint data at the end of Treatment Period 2 (Study Week 25). The outcome of the analysis will inform a decision for the study to continue as the **Original Crossover Design** or switch to the **Contingent Parallel Design**, as follows:

- If data presence ≥85% for 6MWD or actigraphy data at the end of Treatment Period 2 (Study Week 25), the study will continue as planned under the **Original Crossover Design**.
- If data presence <85% for both 6MWD and actigraphy data at the end of Treatment Period 2 (Study Week 25), the study will switch to the **Contingent Parallel Design**.

Adaptation 1 will assess the amount of missing exercise ability data due to subject dropout or otherwise lack of measurement (regardless of onsite or remote) and the outcome will be whether the study continues to completion as the **Original Crossover Design** or the **Contingent Parallel Design.**

Adaptation 2:

Will assess the amount of missing exercise ability data potentially due to the COVID-19 pandemic interfering with onsite measurements. At the conclusion of the study, a blinded analysis will be performed to assess the extent of missing primary efficacy endpoint data (ie, 6MWD data). If the absence of 6MWD data in the Treatment Period, combined across subjects, treatment periods, and key visits (Baseline and Study Week 12) to be used for the final primary endpoint analysis would likely lead to an underpowered study or yield

indeterminate results, a contingent primary endpoint will be used for the final primary endpoint analysis. Such a contingency may include an imputation of missing 6MWD data from actigraphy measurements or the use of actigraphy measurements alone rather than 6MWD for the primary endpoint analysis. This adaptation intends that the 6MWD is to be used as the primary efficacy endpoint for this study, except in the case where onsite measurements for the 6MWD are not reasonably available, and will occur regardless of Adaptation 1 (ie, for either the **Original Crossover Design** or the **Contingent Parallel Design)**. The contingent primary endpoint definition and analysis strategy will be specified a priori with details fully documented in the Statistical Analysis Plan prior to the unblinding of the study.

Original Crossover Design: 8 study visits will be conducted: Screening Visit 1, Screening Visit 2 (upon completion of low dose inhaled treprostinil), and 6 visits during Treatment Periods 1 and 2 (Study Weeks 1, 6, 12, 14, 19, & 25).

Contingent Parallel Design (if applicable): 5 study visits will be conducted: Screening Visit 1, Screening Visit 2 (upon completion of low dose inhaled treprostinil), and 3 visits during the Treatment Period (Study Weeks 1, 6, & 12).

Screening Visit 1 assessments may be spread over multiple days and include initiation of low dose inhaled treprostinil in both the **Original Crossover Design** and the **Contingent Parallel Design**. Subjects will be issued Sponsor-provided actigraphy, spirometry, and smart devices during Screening Visit 1 at the time of treatment initiation to measure at-home activity and FEV_1/FVC. Subjects will be provided proper training on the use of these devices at that time. Subjects who are intolerant of therapy (as determined by the Investigator), unable to follow the dosing regimen, or noncompliant with actigraphy, at-home spirometry, or smart device use during the Screening Period will be ineligible for randomization and deemed screen failures. Subjects may be re-screened (see Section 3.1).

Screening and randomization visits must occur onsite. All attempts should be made to have onsite study visits thereafter. With written Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits after randomization in both the **Original Crossover Design** and the **Contingent Parallel Design,** if the conduct of an onsite study visit poses a safety risk due to the COVID-19 pandemic. See Section 7.4 for the telemedicine visit assessments.

After randomization, study drug dosing will be adjusted to tolerability at the discretion of the Investigator. Study drug dose escalations (additional 1 breath QID) can occur approximately every 3 days with a target dosing regimen of 12 breaths QID or the maximum tolerated dose. Subjects will be contacted at least weekly by telephone during study drug titration and as needed thereafter to provide dosing instructions, assess tolerance to study drug, AEs, device issues, and changes in concomitant medications. Subjects will also be contacted by phone mid-week during the Washout Period(s) to monitor AEs and safety.

An Early Termination (ET) visit will be conducted for subjects who discontinue treatment prior to the end of Treatment Period 2 (Study Week 25) in the **Original Crossover Design** or, if applicable, prior to the end of the Treatment Period (Study Week 12) in the **Contingent**

Parallel Design. All assessments planned for the applicable final study visit will be conducted during the ET Visit.

Key Screening Activities:

- A chest CT scan to evaluate Exclusion Criterion #2 must be performed during the Screening Period. If a chest CT scan was performed within 6 months prior to Screening Visit 1, a repeat assessment is not required. A redacted CT scan report should be provided to the Sponsor's Medical Monitor with the Pre-Baseline Review Form to confirm eligibility.
- An RHC to evaluate Inclusion Criterion #7 must be performed during the Screening Visit 1. If an RHC was performed within 12 months prior to Screening Visit 1, a repeat assessment is not required. For sites seeking guidance on the RHC and oxygen/vasodilator challenge, information is offered as a guide in the Study Procedures Manual, which is provided separately.
- Training on and treatment with low dose inhaled treprostinil to assess tolerability and ability to follow the dosing regimen.
- Training on at-home use of actigraphy, spirometry, and smart devices.

Key Study Activities:

- Pregnancy test: Females of childbearing potential will undergo urine (prior to the first dose of study drug) and serum pregnancy tests during Screening Visit 1 followed by a confirmatory urine pregnancy test at Study Week 1. Serum pregnancy tests will be administered at all other scheduled visits.
- A 6-Minute Walk Test (6MWT) will be conducted during Screening Visit 1 and Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Screening Visit 1 and Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**.
- Borg dyspnea score assessment will be conducted immediately after each 6MWT.
- Pulse oximetry will be conducted continuously prior to, during, and following each 6MWT.
- Blood for NT-proBNP and clinical laboratory assessments will be obtained during Screening Visits 1 and 2 and Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Screening Visits 1 and 2 and at Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**.
- PFTs will be conducted during Screening Visit 1 and Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Screening Visit 1 and Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**.
- Physical activity as measured by actigraphy will be assessed continuously from the time of low dose inhaled treprostinil initiation through the end of the study with the exception of certain activities of daily living (eg, bathing) or when the actigraph is being charged.
- FEV_1 and FVC data as measured by spirometry will be assessed at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study

Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Spirometry should be performed by the subject at home during the allowable window for each study visit.

- QOL assessments: SGRQ and UCSD SOBQ will be completed at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Training on at-home completion of these QOL assessments will be done after randomization.
- PGA will be completed on the Sponsor-provided smart device at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Training on at-home completion of the PGA will be done as appropriate.
- An ECG will be conducted during Screening Visit 1 and Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Screening Visit 1 and Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design.**
- [redacted]
- [redacted]
- [redacted]

Statistical Considerations: This study is an adaptive study initiated as a crossover study (the **Original Crossover Design)**. However, due to the uncertainty of clinical benefit with inhaled treprostinil exposure in PH-COPD subjects and the ongoing COVID-19 pandemic, there is a possibility of treatment discontinuations and/or missing data due to COVID-19 impeding onsite visits, which may render estimates for efficacy outcomes inefficient or biased, thus an automatic switch to the **Contingent Parallel Design** or use of an alternative primary endpoint has been incorporated in this protocol. The protocol specifies the algorithm to seamlessly transition to a parallel-group design (**Contingent Parallel Design**) if the degree of missing data subsequent to subject treatment crossover is not tolerable for primary analysis. Similarly, this protocol specifies that the primary endpoint may be modified if the COVID-19 pandemic prevents onsite visits and data collection for the intended 6MWD primary endpoint data. Evaluations of missing data will be performed in a blinded fashion at the conclusion of the study, irrespective of actual efficacy outcomes and any information regarding efficacy outcomes prior to crossover and, as such, will not impact the Type I error rate.

Original Crossover Design: a 2x2 crossover design will have 90% power to detect a placebo-corrected mean change from baseline difference of 30 meters, assuming that the standard deviation of differences is 85 meters and using a 2-group t-test with a 0.01 two-sided significance level with a sample size of 124 subjects (62 in each sequence group). To account

for a discontinuation rate of approximately 10%, the total sample size will be approximately 136 subjects.

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

Sponsor:	United Therapeutics Corp. [redacted]
Study Conducted by:	Lung Biotechnology PBC [redacted]

LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
BP	Blood pressure
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DLCO	Diffusion capacity for carbon monoxide
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DSP	Distance saturation product
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ERA	Endothelin receptor antagonist
ET	Early Termination
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LVEDP	Left ventricular end-diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
MVPA	Moderate to vigorous physical activity
NT-proBNP	N-Terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAPm	Pulmonary artery pressure mean
PAWP	Pulmonary artery wedge pressure
PDE5-I	Phosphodiesterase type 5 inhibitor

PE	Physical examination
PFT	Pulmonary function test
PGA	Patient global assessment
PH	Pulmonary hypertension
PH-COPD	Pulmonary hypertension due to chronic obstructive pulmonary disease
PVR	Pulmonary vascular resistance
QID	4 times daily
QOL	Quality of life
QRS	Electrocardiographic wave
RHC	Right heart catheterization
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sGC	Soluble guanylate cyclase
SGRQ	St. George's Respiratory Questionnaire
SpO_2	Saturation peripheral capillary oxygenation
TLC	Total lung capacity
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
US	United States
UTC	United Therapeutics Corporation
V/Q	Ventilation/perfusion
WHO	World Health Organization

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1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary hypertension (PH) is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR). The World Health Organization (WHO) classifies PH due to lung diseases and/or hypoxemia as WHO Group 3 PH (Simonneau 2019). This classification includes PH due to chronic obstructive pulmonary disease (PH-COPD).

Chronic obstructive pulmonary disease (COPD) is the most common parenchymal lung disease associated with WHO Group 3 PH (Simonneau 2013, Shino 2013). Reports on the prevalence of PH in COPD are variable (ranging from 30% to 70% with a pulmonary artery pressure mean [PAPm] >20 mmHg) depending on the definition of PH and severity of COPD (Minai 2010). The proportion of patients having COPD with severe PH (PAPm ≥35 mmHg) was reported at 13.5% (Thabut 2005) and 5.8% (Chaouat 2005). The survival rate at 5 years in COPD patients with PH (PAPm >25 mmHg) ranges from 20% to 36% compared with 62% to 66% in COPD patients with normal PAPm (Burger 2009, Chaouat 2005, Oswald-Mammosser 1995).

Potential mechanisms for PH-COPD include vasoconstriction secondary to hypoxia in the pulmonary vasculature, smooth muscle proliferation and vascular remodeling resulting in narrowing of the vascular lumen, and reduction in the total number of pulmonary vessels (Chaouat 2008). Pulmonary hypertension typically appears with severe airflow limitation and is associated with hypoxemia. Pulmonary hypertension due to COPD is most commonly mild to moderate in severity (PAPm 25 to 35 mmHg) (McLaughlin 2009, Klinger 2016, Seeger 2013). A small subset of patients with COPD develop severe PH (PAPm >35 mmHg) despite absence of major airflow limitation (Chaouat 2008, Weitzenblum 2009, Zakynthinos 2011). A PAPm >35 mmHg in patients with COPD is associated with rapid deterioration and increased mortality (Zakynthinos 2011).

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 pulmonary arterial hypertension (PAH) following either the subcutaneous, intravenous, inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

Prostacyclin is known to lower pulmonary artery pressure, increase cardiac output without affecting the heart rate (HR), improve systemic oxygen transport, and possibly reverse pulmonary arterial remodeling. There is increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells, along with vasodilation, may contribute to the therapeutic effects of prostacyclin in the treatment of PAH. Treprostinil acts by triggering direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induces concentration dependent relaxation of rabbit isolated pre-contracted mesenteric arteries and inhibits 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 (US), Argentina, and Israel for the treatment of PAH (WHO Group 1) in patients with New York Heart Association (NYHA) Functional Classification III symptoms, to increase exercise ability.

1.2.2 General Toxicology

A well-defined clinical safety profile exists for treprostinil sodium; acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies have been performed in both rats and dogs and support the chronic administration to patients (Remodulin® Package Insert 2014). The toxicokinetic profile of treprostinil was also evaluated in acute and repeat-dose toxicity studies of up to 13 weeks in duration in rodents and dogs, which supported the chronic administration of inhaled treprostinil to patients. In addition, a 2-year rat carcinogenicity study was performed with treprostinil inhalation at target doses up to 5.26, 10.6, and 34.1 mcg/kg/day, which found no evidence for carcinogenic potential associated with inhaled treprostinil in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. Refer to the Inhaled Treprostinil Investigator's Brochure for a full description of nonclinical data.

1.2.3 Clinical Experience

A series of acute and chronic investigator-initiated clinical studies were conducted with inhaled treprostinil to optimize the formulation for inhalation; determine dose response, tolerability, and safety; and 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 3 study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil in combination with approved PAH therapies. Two hundred thirty-five subjects who were clinically stable on an approved background oral PAH therapy (bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by 6-Minute Walk Distance (6MWD). At Week 12, subjects receiving inhaled treprostinil had a median improvement of +21.6 meters in 6MWD and subjects in the placebo group had a median improvement of +3.0 meters. The Hodges-Lehmann placebo-corrected median change from baseline in peak 6MWD was +20.0 meters (p=0.00044). The durability of this result was supported by secondary measures related to the trough 6MWD, which was measured at least 4 hours after the last dose of inhaled treprostinil. At Week 12, trough 6MWD showed a placebo-corrected median treatment effect of 13.7 meters (p=0.0066). The most commonly reported adverse events (AEs) in the inhaled treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment-related changes in vital signs, physical examination (PE) findings, chest x-rays, pulmonary function tests (PFTs), or clinical laboratory parameters (McLaughlin 2010).

An open-label, extension study of the TRIUMPH-I study to evaluate the use of long-term inhaled treprostinil therapy was also conducted (TRIUMPH-OL). Subjects received 1 to 12 breaths (6 to 72 mcg) 4 times daily (QID) 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 was 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 1- and 2-year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the study. The most frequently reported AEs during the open-label study were cough (39%), headache (31%), upper respiratory tract infection (22%), and nausea (22%). There were no clinically significant changes in clinical chemistry or hematology parameters. Unique findings related to the inhaled route of administration, in addition to cough, were throat pain and throat irritation, occurring in 12% and 10% of subjects, respectively. These events were usually of mild or moderate severity and transient in duration. In a few subjects, these specific AEs were more pronounced, as 6 subjects (3%) discontinued inhaled treprostinil due to cough, including 1 subject (<1%) with dry throat (Benza 2011).

1.3 RATIONALE FOR DEVELOPMENT OF INHALED TREPROSTINIL IN DISEASE/CONDITION

Currently, there are no approved therapies for the treatment of PH-COPD. Since this condition is associated with increased mortality compared to patients with COPD alone, PH management is vital for improving overall survival and decreasing associated PH-related symptoms (Klinger 2016).

Pulmonary arterial hypertension (WHO Group 1 PH) has similar disease mechanisms to PH-COPD (ie, vasoconstriction, smooth muscle cell proliferation, vascular remodeling), which suggests that PAH-specific therapies, specifically vasodilators, may be valuable treatments for PH-COPD. Approved therapies for PAH include endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5-Is), soluble guanylate cyclase (sGC) stimulators, prostacyclin receptor agonists, and prostacyclin analogs. These therapies work to treat PAH through multiple mechanisms with vasodilation being a primary mode of action. Preliminary evidence in several small PH-COPD studies of PAH-specific therapies supports this hypothesis and suggests that a systematic evaluation of this treatment strategy is warranted (Klinger 2016).

1.4 CLINICAL HYPOTHESIS

There is unclear evidence for clinical benefit in PH-COPD with the use of oral vasodilators, such as ERAs, PDE5-Is, and sGC stimulators.

This may be attributed to worsening of the ventilation/perfusion (V/Q) ratio as a result of systemic vasodilation. In PH-COPD, the presence of local hypoxia results in vasoconstriction, which helps to distribute the blood flow to better-ventilated portions of the lung and improves the V/Q ratio. The administration of systemic vasodilators in the treatment of PH-COPD is thought to confound this mechanism, resulting in worsening gas exchange, despite reported improvements in hemodynamic parameters (Archer 1996, Blanco 2010, Stolz 2008). In contrast, inhaled vasodilators are expected to directly target the more ventilated portion of the lungs in patients with PH-COPD, minimizing the risk of V/Q mismatch and allowing for improvements in exercise capacity (Seeger 2013).

Inhaled treprostinil (Tyvaso) is approved and registered as an effective inhaled prostacyclin treatment for PAH with an acceptable safety profile. Treprostinil is a stable tricyclic benzindene analogue of the naturally occurring prostacyclin, PGI2 (epoprostenol). Prostacyclins are known to lower pulmonary artery pressure, increase cardiac output without affecting the HR, improve systemic oxygen transport, and possibly reverse pulmonary arterial remodeling. There is increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells, along with vasodilation, may contribute to the therapeutic effects of prostacyclin in the treatment of PAH. Hence, the mechanism of action of treprostinil is theorized to be multifactorial, with the major pharmacological actions of treprostinil being direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Several early phase studies have evaluated the use of inhaled prostacyclin analogs in patients with PH-COPD (Klinger 2016). In small observational studies evaluating the administration of inhaled treprostinil in patients with PH-COPD, trends to improvement in 6MWD were noted, with other measures of blood gases showing inconsistent results (Malik 2013, Agarwal 2015, Anderson 2017, Bajwa 2017, Faria-Urbina 2018). The reported improvements in exercise ability and preserved oxygenation seen in the above preliminary studies suggest that inhaled treprostinil can be well tolerated and potentially effective in the PH-COPD patient population.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate the efficacy of inhaled treprostinil compared to placebo in improving exercise ability as measured by change from baseline in 6MWD following 12 weeks of active treatment in subjects with PH-COPD.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to assess the effect of inhaled treprostinil compared to placebo after 12 weeks of active treatment on the following:

1. Change in moderate to vigorous physical activity (MVPA) as measured by actigraphy
2. Change in overall activity as measured by actigraphy
3. Change in Borg dyspnea score from baseline
4. Change in 6MWD/Borg dyspnea composite score from baseline
5. Change in QOL from baseline as measured by St. George's Respiratory Questionnaire (SGRQ) and the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)
6. Change in plasma concentration of N-Terminal pro-brain natriuretic peptide (NT-proBNP) from baseline
7. Change in patient global assessment (PGA)

2.3 SAFETY OBJECTIVES

The safety of inhaled treprostinil in comparison to placebo will be evaluated on the following:

1. AEs
2. Clinical laboratory assessments
3. Electrocardiograms (ECGs)
4. Physical examination (PE) findings
5. Oxygenation
6. PFTs
7. Vital sign measurements
8. At-home spirometry

2.4 EXPLORATORY OBJECTIVES

[redacted]

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, 34-week, crossover study with a Treatment Period of approximately 26 weeks under the **Original Crossover Design** or, if applicable, a 21-week parallel study with a Treatment Period of approximately 14 weeks under the **Contingent Parallel Design**. All randomized subjects will be treated with active drug and placebo in the **Original Crossover Design** or, if applicable, active drug or placebo in the **Contingent Parallel Design**.

Screening and randomization visits must occur onsite. All attempts should be made to have onsite study visits thereafter. With written Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits after randomization, in both the **Original Crossover Design** and the **Contingent Parallel Design**, if the conduct of an onsite study visit poses a safety risk due to the COVID-19 pandemic. See Section 7.4 for the telemedicine visit assessments.

The study will consist of the following periods:

Screening Period: During Screening Visit 1, prospective subjects (such as those having prior echocardiogram findings of right ventricular systolic pressure >40 mmHg and/or evidence of right ventricular hypertrophy or dysfunction) who sign the Informed Consent Form (ICF) will generally undergo all non-invasive screening assessments to evaluate eligibility as listed in the inclusion/exclusion criteria. Potentially eligible subjects will undergo right heart catheterization (RHC), which should include a vasodilator test and oxygen challenge, if possible. For sites seeking guidance on the RHC and oxygen/vasodilator challenge, information is offered as a guide in the Study Procedures Manual, which is provided separately.

If RHC results are available from a test performed within the previous 12 months (even if done without oxygen or vasodilator challenge), a repeat RHC during Screening Visit 1 is not needed.

A window of up to 6 weeks is permitted to complete all assessments required for Screening Visit 1, including the start of low dose inhaled treprostinil. Prospective subjects meeting all eligibility criteria will be provided with and trained on inhalation of study drug using the Tyvaso Inhalation System and begin low dose (3 breaths QID) inhaled treprostinil for a minimum of 14 days (maximum of 18 days) to ensure tolerability and compliance. Subjects will be issued Sponsor-provided actigraphy, spirometry, and smart devices during Screening Visit 1 at the time of low dose inhaled treprostinil initiation for measurement of at-home activity and forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC). Subjects will be given training on the at-home use of these devices, as well as Instructions for Use. At Screening Visit 2, subjects will return to the study site following completion of low dose inhaled treprostinil exposure to undergo scheduled assessments and return unused study drug. Subjects who are intolerant of therapy (as determined by the Investigator), unable to follow the dosing regimen, or noncompliant with actigraphy, at-home spirometry, or smart device use during the Screening Period will be ineligible for randomization and deemed screen failures.

Re-screening: Subjects may be re-screened. The study-specific RHC performed during Screening Visit 1 is valid for up to 12 months and should not be repeated if a subject is re-screened unless written approval is first obtained from the Sponsor's Medical Monitor.

Original Crossover Design:

Washout Period - Washout 1: During Washout 1 (Study Week -1), prospective subjects will refrain from the use of inhaled treprostinil for a minimum of 7 days (maximum of 14 days) preceding entry into the Treatment Period 1 Baseline Visit (Study Week 1). Subjects will be contacted by telephone mid-week in Washout Period 1 to monitor safety.

Treatment Period 1: Eligible subjects approved by the Sponsor's Medical Monitor will undergo Treatment Period 1 Baseline Visit assessments (Study Week 1), be assigned to a treatment group based on the randomization schedule, and receive study drug. Target dosing with study drug (after titration) will be 12 breaths QID or to maximum tolerated dose.

Two additional study visits to the study site will be conducted after the Treatment Period 1 Baseline Visit to complete study assessments (Study Weeks 6 & 12). Subjects will be contacted weekly by telephone during study drug titration (until 12 breaths QID or the maximum tolerated dose is achieved) and as needed thereafter to provide dosing instructions and to assess tolerance to study drug, AEs, and changes in concomitant medications.

Washout Period - Washout 2: Subjects will refrain from the use of study drug for a minimum of 7 days (maximum of 14 days) after the Treatment Period 1 Week 12 Visit (Study Week 12) and preceding entry into Treatment Period 2 (Study Week 14). Subjects will be contacted by telephone mid-week in Washout Period 2 to monitor safety.

Treatment Period 2: Subjects will undergo Treatment Period 2 Baseline Visit assessments (Study Week 14), be provided treatment based on the randomization schedule, and receive study drug for this period. Target dosing with study drug (after titration) will be 12 breaths QID or to the maximum tolerated dose. Two additional study visits to the study site (Study Weeks 19 & 25) will be conducted after the Treatment Period 2 Baseline Visit (Study Week 14) to complete study assessments. Subjects will be contacted weekly by telephone during study drug titration (until 12 breaths QID or the maximum tolerated dose is achieved) and as needed thereafter to provide dosing instructions and to assess tolerance to study drug, AEs, and changes in concomitant medications. At the completion of Treatment Period 2 (Study Week 25), subjects will be offered enrollment in the open-label extension study, RIN-PH-305. If the Sponsor adapts the study to the **Contingent Parallel Design**, any subject in Treatment Period 2 at that time will be asked to return to the site for an Early Termination (ET) Visit and will be offered enrollment in the open-label extension study, RIN-PH-305.

Contingent Parallel Design (If Applicable):

Washout Period: During Washout (Study Week -1), prospective subjects will refrain from the use of inhaled treprostinil for a minimum of 7 days (maximum of 14 days) preceding entry into the Baseline Visit (Study Week 1). Subjects will be contacted by telephone mid-week in the Washout Period to monitor safety.

Treatment Period: Eligible subjects that have undergone the previously described Screening Period and are approved by the Sponsor for enrollment will undergo Baseline Visit assessments (Study Week 1), be assigned to a treatment group based on the randomization schedule, and receive study drug. Target dosing with study drug (after titration) will be 12 breaths QID or to the maximum tolerated dose. Two additional study visits to the study site will be conducted after the Baseline Visit to complete study assessments (Study Weeks 6 & 12). Subjects will be contacted weekly by telephone during study drug titration (until 12 breaths QID or the maximum tolerated dose is achieved) and as needed thereafter to provide dosing instructions and to assess tolerance to study drug, AEs, and changes in concomitant medications. At the completion of the Treatment Period (Study Week 12), subjects will be offered enrollment in the open-label extension study, RIN-PH-305.

Early Termination: An ET Visit will be conducted for subjects who end participation in the study prior to the completion of Treatment Period 2 (Study Week 25) in the **Original Crossover Design** or, if applicable, prior to the end of the Treatment Period (Study Week 12) in the **Contingent Parallel Design**. All assessments planned for the applicable final study visits will be conducted during the ET Visit.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

3.2.1 Original Crossover Design Schedule of Times and Events

Table 3-1 Original Crossover Design Overall Schedule of Times and Events

Study Procedures[a]	Screening Period[a]		Washout Period[a]	Treatment Period 1			Washout Period[a]	Treatment Period 2			
	Screening Visit 1	Screening Visit 2	Washout 1	Baseline Visit	Week 6 Visit	Week 12 Visit	Washout 2	Baseline Visit	Week 19 Visit	Week 25 Visit	Early Termination
Study Week	**-9 to -3**	**-2**	**-1**	**1**	**6**	**12**	**13**	**14**	**19**	**25**	**N/A**
Study Day	**-63 to -22**	**-8 (or -4)**	**-7 to -1[a]**	**1**	**42±3**	**84±3**	**85 to 91[a]**	**92±3**	**133±3**	**175±3**	**N/A**
Site Visit	**X**	**X**	**N/A**	**X**	**X**	**X**	**N/A**	**X**	**X**	**X**	**X**
Informed Consent	X[u]										
Demographics	X[u]										
Medical History	X[u]										
Physical Examination[v,x]	X[u]	X		X[u]	X	X		X[u]	X	X	X
Vital Signs[b,v,x]	X[u]	X		X[u]	X	X		X[u]	X	X	X
12-Lead ECG[b,v,x]	X[u]			X[u]	X	X		X[u]	X	X	X
Clinical Laboratory Assessments[x]	X[u]	X		X[u]	X	X		X[u]	X	X	X
NT-proBNP[c,x]	X[u]	X		X[u]	X	X		X[u]	X	X	X
Pregnancy Test[d,x]	X[u]			X[u]	X	X		X[u]	X	X	X
6MWT[e,x]	X[u]			X[u]	X	X		X[u]	X	X	X
Actigraphy[w]	X	X	X	X	X	X	X	X[u]	X	X	X
Pulse Oximetry[f,x]	X[u]			X[u]	X	X		X[u]	X	X	X
Borg Dyspnea Score[g,x]	X[u]			X[u]	X	X		X[u]	X	X	X
PFTs[h,x]	X[u]			X[u]	X	X		X[u]	X	X	X
At-home spirometry[y]	X	X		X[u]	X	X		X[u]	X	X	X
CT Scan[i]	X[u]										

Study Procedures[a]	**Screening Period[a]**		**Washout Period[a]**	**Treatment Period 1**			**Washout Period[a]**	**Treatment Period 2**			
	Screening Visit 1	**Screening Visit 2**	**Washout 1**	**Baseline Visit**	**Week 6 Visit**	**Week 12 Visit**	**Washout 2**	**Baseline Visit**	**Week 19 Visit**	**Week 25 Visit**	**Early Termination**
Study Week	**-9 to -3**	**-2**	**-1**	**1**	**6**	**12**	**13**	**14**	**19**	**25**	**N/A**
Study Day	**-63 to -22**	**-8 (or -4)**	**-7 to -1[a]**	**1**	**42±3**	**84±3**	**85 to 91[a]**	**92±3**	**133±3**	**175±3**	**N/A**
Site Visit	**X**	**X**	**N/A**	**X**	**X**	**X**	**N/A**	**X**	**X**	**X**	**X**
RHC[j]	X[u]										
Study Drug and Dosing Instructions	X			X	X			X	X		
Drug Administration at Site	X[k]			X[x]	X[x]	X[x]		X[x]	X[x]	X[x]	
Device Training[k]	X										
Adverse Events[l]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[m]	X	X	X	X	X	X	X	X	X	X	X
Weekly Contact[n]	X	X	X	X	X	X	X	X	X	X	
QOL[o]				X[u]	X	X		X[u]	X	X	X
PGA[z]				X	X	X		X[u]	X	X	X
Subject Eligibility	X[u]	X		X[u]							
Pre-Baseline Review Form[p]		X									
Randomization[q]				X							
Drug/Device Accountability[x]		X			X	X			X	X	X
[redacted]											

Study Procedures[a]	Screening Period[a]		Washout Period[a]	Treatment Period 1			Washout Period[a]	Treatment Period 2			
	Screening Visit 1	Screening Visit 2	Washout 1	Baseline Visit	Week 6 Visit	Week 12 Visit	Washout 2	Baseline Visit	Week 19 Visit	Week 25 Visit	Early Termination
Study Week	-9 to -3	-2	-1	1	6	12	13	14	19	25	N/A
Study Day	-63 to -22	-8 (or -4)	-7 to -1[a]	1	42±3	84±3	85 to 91[a]	92±3	133±3	175±3	N/A
Site Visit	X	X	N/A	X	X	X	N/A	X	X	X	X
[redacted]											

6MWT, 6-Minute Walk Test; AE, adverse event; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eCRF, electronic Case Report Form; ET, early termination; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; N/A, not applicable; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PFT, pulmonary function test; PGA, patient global assessment; QOL, quality of life; RHC, right heart catheterization; RNA, ribonucleic acid; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire; SpO_2, saturation peripheral capillary oxygenation; TLC, total lung capacity; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire

[a] Sites may schedule non-invasive screening assessments, RHC, and study drug start on different days to facilitate scheduling. However, study drug exposure in the Screening Period must be for a minimum of 14 days (maximum of 18 days) and washout must be for a minimum of 7 days (maximum 14 days). If deemed necessary, per the clinical judgement of the site staff or Investigator, subjects may be asked to return to the study site for an unscheduled visit to assess their status. This visit may require blood draws, vital signs, and/or review of concomitant medications. Any assessments performed at an unscheduled visit should be recorded in the source documents and reported in the appropriate eCRF pages.

[b] Vital signs and ECG must be performed after a 5-minute period of rest (seated rest for vital signs). No other procedures should be conducted during the rest period. When possible, vital signs should be collected prior to the 6MWT. Height will be measured and recorded only during Screening Visit 1.

[c] Blood for the NT-proBNP assessment must be drawn prior to conducting the 6MWT and dosing of study drug during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**.

[d] For females of childbearing potential. Urine (prior to the first dose of study drug) and serum pregnancy tests at Screening Visit 1 and a urine pregnancy test at Study Week 1. Serum pregnancy tests will be performed at all other scheduled visits.

[e] The Screening Visit 1 6MWTs must precede open-label treprostinil dosing. The 6MWT at Study Week 1 must be performed after randomization, but before administration of study drug, and the 6MWT at Study Week 14 must be performed before administration of study drug. All other post-randomization 6MWTs will be performed between 10 and 60 minutes after study drug has been administered at the study site. Prior to the start of each 6MWT, the subject should rest (seated) for at least 10 minutes. Subjects receiving supplemental oxygen during any pre-randomization 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable. If the site or subject has implemented protective measures against COVID-19, all subsequent 6MWT assessments should be made in a generally consistent manner.

[f] Pulse oximetry to be performed continuously prior to, during, and following each 6MWT. Pulse oximetry will include the measurement of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the source documents and eCRF. The lowest recorded SpO_2 obtained during each 6MWT (and associated HR) will be recorded in the source documents and eCRF.

[g] See Appendix 15.2. The subject should be asked to rate their maximal breathlessness during the 6MWT.

[h] PFTs will include the evaluation of FEV_1, FVC, TLC, and DLCO. TLC and DLCO will be assessed only when clinically feasible. PFTs should be conducted either before the 6MWT or after recovering from the 6MWT. If the PFTs are done both pre-bronchodilator and post-bronchodilator administration, only the post-bronchodilator treatment values will be recorded.

[i] This CT scan is required for Exclusion Criterion #2. A chest CT scan performed within 6 months prior to the start of Screening Visit 1 is acceptable and a repeat assessment is not required.

[j] The RHC procedure details are provided in the Study Procedures Manual, but the RHC may be omitted if it was performed within 12 months of the start of Screening Visit 1, even if vasodilator test and/or oxygen challenge were not completed. Results from a previous RHC should be added to source records and entered in the eCRF. RHC parameters, including PAPm, PVR, and PAWP (or LVEDP), and if available, pressures with and without oxygen, and vasodilator response are to be recorded.

[k] If all study eligibility criteria are met, dosing instructions and device training will occur, followed by administration of study drug. The subject must remain at the study site for observation at least 1 hour after the first dose of study drug is administered during Screening Visit 1.

[l] All AEs/SAEs will be documented from the time of informed consent until the time screen failure is documented, study completion, or ET. All AEs/SAEs should be followed as outlined in Section 9.3.

[m] The amount of supplemental oxygen (L/min) required at rest will be assessed at all scheduled visits and recorded on the concomitant medication eCRF.

[n] At least weekly telephone contact is required during study drug titration (until 12 breaths QID or the maximum tolerated dose is achieved) and as needed thereafter. Face-to-face interaction may replace the telephone contact on the weeks where onsite study visits occur, and the information can be obtained during the onsite visit. During the Washout Periods, the telephone contact will occur mid-week between study visits. A copy of the telephone contact sheets must be kept in the subject's source documentation.

[o] After randomization, site staff will provide subjects paper copies of the QOL questionnaires and training on at-home completion, in the event telemedicine visits are needed thereafter. Site staff should only use the paper copies of the questionnaires provided by the Sponsor. The SGRQ and UCSD SOBQ QOL assessments that are completed by the subject at home will be returned to the site as instructed by the site staff.

[p] Sites should complete the Pre-Baseline Review Form, confirm tolerability and compliance of study drug during the Screening Period, and request the Sponsor's Medical Monitor to review subject eligibility and allow randomization. Subject randomization will not be possible until the Pre-Baseline Review Form (and supporting documentation) is complete and the Sponsor's Medical Monitor approves the subject.

[q] Once all entry criteria have been met and the randomized treatment assigned, the first dose of study drug (3 breaths) will be inhaled at the study site.

[redacted]

[u] This assessment to be performed before study drug is administered.

[v] Any clinically significant changes from Screening Visit 1 should be reported as AEs.

[w] Subjects will be issued a Sponsor-provided actigraph (activity monitor) during Screening Visit 1 at the time of low dose inhaled treprostinil initiation to measure daily at-home physical activity. Subjects will be required to wear the device continuously from this visit through the end of the study, with the exception of certain activities of daily living (eg, bathing) or when the actigraph is being charged. Subjects will be given specific instructions on how to perform actigraphy, in addition to a copy of the Instructions for Use. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

[x] Applicable only if an onsite study visit.

[y] Subjects will be issued a Sponsor-provided spirometry device during Screening Visit 1 at the time of low dose inhaled treprostinil initiation for at-home capture of FEV_1 and FVC data. Subjects will be given specific instructions on how to perform the spirometry assessment, in addition to a copy of the Instructions for Use. Subjects will be asked to perform the spirometry assessment at home during the allowable window for each study visit. Subjects are encouraged to complete the activity ahead of their scheduled visit. If spirometry is not performed prior to a visit, the subject should perform the spirometry assessment during the visit. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

[z] Subjects will use the Sponsor-provided smart device for at-home capture of PGA data at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Subjects will be asked to perform the PGA at the same time as the at-home spirometry assessment at all applicable visits. Subjects are encouraged to complete the activity ahead of their scheduled visit. If the PGA is not performed prior to a visit, the subject should perform the PGA during the visit. Assessment of proper use and data capture should be performed by the site staff at all applicable visits.

3.2.2 Contingent Parallel Design (if Applicable) Schedule of Times and Events

Table 3-2 Contingent Parallel Design Overall Schedule of Times and Events

Study Procedures[a]	Screening Period[a]		Washout Period[a]	Treatment Period			
	Screening Visit 1	Screening Visit 2	Washout	Baseline Visit	Week 6 Visit	Week 12 Visit	Early Termination
Study Week	**-9 to -3**	**-2**	**-1**	**1**	**6**	**12**	**N/A**
Study Day	**-63 to -22**	**-8 (or -4)**	**-7 to -1**	**1**	**42±3**	**84±3**	**N/A**
Site Visit	**X**	**X**	**N/A**	**X**	**X**	**X**	**X**
Informed Consent	X[u]						
Demographics	X[u]						
Medical History	X[u]						
Physical Examination[v,x]	X[u]	X		X[u]	X	X	X
Vital Signs[b,v,x]	X[u]	X		X[u]	X	X	X
12-Lead ECG[b,v,x]	X[u]			X[u]	X	X	X
Clinical Laboratory Assessments[x]	X[u]	X		X[u]	X	X	X
NT-proBNP[c,x]	X[u]	X		X[u]	X	X	X
Pregnancy Test[d,x]	X[u]			X[u]	X	X	X
6MWT[e,x]	X[u]			X[u]	X	X	X
Actigraphy[w]	X	X	X	X	X	X	X
Pulse Oximetry[f,x]	X[u]			X[u]	X	X	X
Borg Dyspnea Score[g,x]	X[u]			X[u]	X	X	X
PFTs[h,x]	X[u]			X[u]	X	X	X
At-home spirometry[y]	X	X		X[u]	X	X	X
CT Scan[i]	X[u]						
RHC[j]	X[u]						
Study Drug and Dosing Instructions	X			X	X		

Study Procedures[a]	Screening Period[a]		Washout Period[a]	Treatment Period			
	Screening Visit 1	Screening Visit 2	Washout	Baseline Visit	Week 6 Visit	Week 12 Visit	Early Termination
Study Week	**-9 to -3**	**-2**	**-1**	**1**	**6**	**12**	**N/A**
Study Day	**-63 to -22**	**-8 (or -4)**	**-7 to -1**	**1**	**42±3**	**84±3**	**N/A**
Site Visit	**X**	**X**	**N/A**	**X**	**X**	**X**	**X**
Drug Administration at Site	X[k]			X[x]	X[x]	X[x]	
Device Training[k]	X						
Adverse Events[l]	X	X	X	X	X	X	X
Concomitant Medications[m]	X	X	X	X	X	X	X
Weekly Contact[n]	X	X	X	X	X	X	
QOL[o]				X[u]	X	X	X
PGA[z]				X	X	X	X
Subject Eligibility	X[u]	X		X[u]			
Pre-Baseline Review Form[p]		X					
Randomization[q]				X			
Drug/Device Accountability[x]		X			X	X	X
[redacted]							

6MWT, 6-Minute Walk Test; AE, adverse event; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eCRF, electronic Case Report Form; ET, early termination; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; N/A, not applicable; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PFT, pulmonary function test; PGA, patient global assessment; QOL, quality of life; RHC, right heart catheterization; RNA, ribonucleic acid; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire; SpO_2, saturation peripheral capillary oxygenation; TLC, total lung capacity; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire

[a] Sites may schedule non-invasive screening assessments, RHC, and study drug start on different days to facilitate scheduling. However, study drug exposure in the Screening Period must be for a minimum of 14 days (maximum of 18 days) and washout must be for a minimum of 7 days (maximum 14 days). If deemed necessary, per the clinical judgement of the site staff or Investigator, subjects may be asked to return to the study site for an unscheduled visit to assess their status. This visit may require blood draws, vital signs, and/or review of concomitant medications. Any assessments performed at an unscheduled visit should be recorded in the source documents and reported in the appropriate eCRF pages.

[b] Vital signs and ECG must be performed after a 5-minute period of rest (seated rest for vital signs). No other procedures should be conducted during the rest period. When possible, vital signs should be collected prior to the 6MWT. Height will be measured and recorded only during Screening Visit 1.

[c] Blood for the NT-proBNP assessment must be drawn prior to conducting the 6MWT and dosing of study drug during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**.

[d] For females of childbearing potential. Urine (prior to the first dose of study drug) and serum pregnancy tests at Screening Visit 1 and a urine pregnancy test at Study Week 1. Serum pregnancy tests will be performed at all other scheduled visits.

[e] The Screening Visit 1 6MWTs must precede open-label treprostinil dosing. The 6MWT at Study Week 1 must be performed after randomization, but before administration of study drug. All other post-randomization 6MWTs will be performed between 10 and 60 minutes after study drug has been administered at the study site. Prior to the start of each 6MWT, the subject should rest (seated) for at least 10 minutes. Subjects receiving supplemental oxygen during any pre-randomization 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable. If the site or subject has implemented protective measures against COVID-19, all subsequent 6MWT assessments should be made in a generally consistent manner.

[f] Pulse oximetry to be performed continuously prior to, during, and following each 6MWT. Pulse oximetry will include the measurement of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the source documents and eCRF. The lowest recorded SpO_2 obtained during each 6MWT (and associated HR) will be recorded in the source documents and eCRF.

[g] See Appendix 15.2. The subject should be asked to rate their maximal breathlessness during the 6MWT.

[h] PFTs will include the evaluation of FEV_1, FVC, TLC, and DLCO. TLC and DLCO will be assessed only when clinically feasible. PFTs should be conducted either before the 6MWT or after recovering from the 6MWT. If the PFTs are done both pre-bronchodilator and post-bronchodilator administration, only the post-bronchodilator treatment values will be recorded.

[i] This CT scan is required for Exclusion Criterion #2. A chest CT scan performed within 6 months prior to the start of Screening Visit 1 is acceptable and a repeat assessment is not required.

[j] The RHC procedure details are provided in the Study Procedures Manual, but the RHC may be omitted if it was performed within 12 months of the start of Screening Visit 1, even if vasodilator test and/or oxygen challenge were not completed. Results from a previous RHC should be added to source records and entered in the eCRF. RHC parameters, including PAPm, PVR, and PAWP (or LVEDP), and if available, pressures with and without oxygen, and vasodilator response are to be recorded.

[k] If all study eligibility criteria are met, dosing instructions and device training will occur, followed by administration of study drug. The subject must remain at the study site for observation at least 1 hour after the first dose of study drug is administered during Screening Visit 1.

[l] All AEs/SAEs will be documented from the time of informed consent until the time screen failure is documented, study completion, or ET. All AEs/SAEs should be followed as outlined in Section 9.3.

[m] The amount of supplemental oxygen (L/min) required at rest will be assessed at all scheduled visits and recorded on the concomitant medication eCRF.

[n] At least weekly telephone contact is required during study drug titration (until 12 breaths QID or the maximum tolerated dose is achieved) and as needed thereafter. Face-to-face interaction may replace the telephone contact on the weeks where onsite study visits occur, and the information can be obtained during the onsite visit. During the Washout Period, the telephone contact will occur mid-week between study visits. A copy of the telephone contact sheets must be kept in the subject's source documentation.

[o] After randomization, site staff will provide subjects paper copies of the QOL questionnaires and training on at-home completion, in the event telemedicine visits are needed thereafter. Site staff should only use the paper copies of the questionnaires provided by the Sponsor. The SGRQ and UCSD SOBQ QOL assessments that are completed by the subject at home will be returned to the site as instructed by the site staff.

[p] Sites should complete the Pre-Baseline Review Form, confirm tolerability and compliance of study drug during the Screening Period, and request the Sponsor's Medical Monitor to review subject eligibility and allow randomization. Subject randomization will not be possible until the Pre-Baseline Review Form (and supporting documentation) is complete and the Sponsor's Medical Monitor approves the subject.

[q] Once all entry criteria have been met and the randomized treatment assigned, the first dose of study drug (3 breaths) will be inhaled at the study site.

[redacted]

[u] This assessment to be performed before study drug is administered.

[v] Any clinically significant changes from Screening Visit 1 should be reported as AEs.

[w] Subjects will be issued a Sponsor-provided actigraph (activity monitor) during Screening Visit 1 at the time of low dose inhaled treprostinil initiation to measure daily at-home physical activity. Subjects will be required to wear the device continuously from this visit through the end of the study, with the exception of certain activities of daily living (eg, bathing) or when the actigraph is being charged. Subjects will be given specific instructions on how to perform actigraphy, in addition to a copy of the Instructions for Use. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

[x] Applicable only if an onsite study visit.

[y] Subjects will be issued a Sponsor-provided spirometry device during Screening Visit 1 at the time of low dose inhaled treprostinil initiation for at-home capture of FEV_1 and FVC data. Subjects will be given specific instructions on how to perform the spirometry assessment, in addition to a copy of the Instructions for Use. Subjects will be asked to perform the spirometry assessment at home during the allowable window for each study visit. Subjects are encouraged to complete the activity ahead of their scheduled visit. If spirometry is not performed prior to a visit, the subject should perform the spirometry assessment during the visit. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

[z] Subjects will use the Sponsor-provided smart device for at-home capture of PGA data at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Subjects will be asked to perform the PGA at the same time as the at-home spirometry assessment at all applicable visits. Subjects are encouraged to complete the activity ahead of their scheduled visit. If the PGA is not performed prior to a visit, the subject should perform the PGA during the visit. Assessment of proper use and data capture should be performed by the site staff at all applicable visits.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

The efficacy of inhaled treprostinil compared to placebo will be evaluated on the following parameters: change in 6MWD measured at peak exposure (defined as 10 to 60 minutes after dosing) after 12 weeks of treatment, change in MVPA as measured by actigraphy, change in overall activity as measured by actigraphy, change in Borg dyspnea score from baseline, change in 6MWD/Borg dyspnea composite score from baseline, change in QOL from baseline as measured by SGRQ and the UCSD SOBQ, change in plasma concentration of NT-proBNP from baseline, and change in PGA.

3.3.1.1 St. George's Respiratory Questionnaire and the University of California San Diego Shortness of Breath Questionnaire

The SGRQ is designed to measure impact on overall health, daily life, and perceived wellbeing in subjects. A copy of the SGRQ can be found in Appendix 15.3.

The UCSD SOBQ is a 24-item dyspnea questionnaire that asks subjects to rate themselves from 0 (none at all) to 5 (maximum or unable to do because of shortness of breath) in 2 areas, 1) how short of breath they are while performing various activities (21 items), and 2) how much shortness of breath limits them in their daily lives (3 items) (Eakin 1998). Scores range from 0 to 120, with higher scores indicating greater shortness of breath. A copy of the UCSD SOBQ can be found in Appendix 15.4.

Both questionnaires will be completed at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design.**

After randomization, site staff will provide subjects paper copies of the QOL questionnaires and training on at-home completion, in the event telemedicine visits are needed thereafter. Site staff should only use the paper copies of the questionnaires provided by the Sponsor. The SGRQ and UCSD SOBQ QOL assessments completed by the subject at home will be returned to the site as instructed by the site staff.

3.3.1.2 Patient Global Assessment (PGA)

The PGA is a being used to rate subject fatigue and shortness of breath. Subjects will use the Sponsor-provided smart device for at-home capture of PGA data at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Subjects will be asked to perform the PGA at the same time as the at-home spirometry assessment at all applicable visits. Subjects are encouraged to complete the activity ahead of their scheduled visit. If the PGA is not performed prior to a visit, the subject should perform the PGA during the visit. Assessment of proper use and data capture should be performed by the site staff at all applicable visits. A copy of the PGA can be found in Appendix 15.5.

3.3.1.3 N-Terminal Pro-brain Natriuretic Peptide

NT-proBNP is a biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). Blood will be collected for assessment of NT-proBNP at all scheduled study visits. Blood must be drawn prior to conducting the 6MWT and prior to study drug dosing during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design**, or if applicable, during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**.

In the event of Sponsor-approved telemedicine visits, NT-proBNP sample collection will not be performed.

3.3.1.4 6-Minute Walk Test

The 6MWT is a validated and reliable measure of exercise ability in patients with chronic respiratory diseases (Holland 2014). This study will utilize an unencouraged 6MWT to minimize potential bias associated with encouragement. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area, which meets the requirements described in Appendix 15.1.

Prior to the start of each 6MWT, the subject must rest (seated) for at least 10 minutes. The 6MWT must be performed prior to study drug dosing during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**. At all other visits, 6MWTs will be performed between 10 and 60 minutes after study drug has been administered at the study site.

Pulse oximetry is to be performed continuously prior to, during, and following each scheduled 6MWT, as outlined in Section 3.3.2.9.

Similarly, if the site or subject has implemented protective measures against COVID-19 (eg, use of an alternative 6MWT testing area or use of personal protective equipment [mask, face shield, etc]) during the pre-randomization 6MWT, all subsequent 6MWT assessments should be made in a generally consistent manner.

In the event of Sponsor-approved telemedicine visits, the 6MWT assessment will not be performed, but the subject will continue to wear an actigraph and maintain normal activity.

3.3.1.4.1 Supplemental Oxygen Use During the 6-Minute Walk Test

Subjects receiving supplemental oxygen during the pre-randomization 6MWTs must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable. Supplemental oxygen therapy must not be introduced for subjects after randomization, unless there is an urgent medical need in the clinical judgement of the Investigator; however, if supplemental oxygen therapy is started post-randomization, the flow should be consistent for all subsequent tests.

3.3.1.5 Borg Dyspnea Score

The Borg dyspnea score is a 0 to 10 scale rating of the level of dyspnea experienced during the 6MWT and is administered immediately following the 6MWT. Scores range from 0 (no shortness of breath) to 10 (maximal shortness of breath). A copy of the Borg dyspnea scale can be found in Appendix 15.2.

In the event of Sponsor-approved telemedicine visits, the Borg dyspnea score assessment will not be performed.

3.3.1.6 Actigraphy

Subjects will be issued a Sponsor-provided actigraph (activity monitor) during Screening Visit 1 at the time of low dose inhaled treprostinil initiation for measurement of daily at-home physical activity. A variety of physical activity parameters, including overall activity, non-sedentary activity, and MVPA will be measured via this wrist-worn medical grade physical activity monitor. The screening data will be used to establish a baseline level of physical activity.

Subjects will be asked to wear the actigraph continuously throughout the study with the exception of certain activities of daily living (eg, bathing) and when the device is being charged. Subjects will be given specific instructions on how to use the actigraph. In addition, subjects will receive a copy of the Instructions for Use. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

3.3.2 Safety

The safety of inhaled treprostinil compared to placebo will be evaluated on the following parameters: AEs, PE findings, vital sign measurements, ECGs, clinical laboratory assessments, PFTs, at-home spirometry, CT (required), concomitant medications, and oxygenation.

3.3.2.1 Medical History and Demographics

A complete medical history (inclusive of PH-COPD) including demographics will be collected pre-dose during Screening Visit 1. Any known changes to the medical history prior to randomization should be recorded in the subject source documents and in the electronic Case Report Form (eCRF). Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs should be recorded also. Any significant changes in the subject's medical condition throughout the course of the study must also be documented in the subject's source documents and in the eCRF.

3.3.2.2 Physical Examinations

A complete PE will be conducted by appropriate study personnel (as documented on the Delegation of Authority Log) at all study visits. Any clinically significant changes from Screening Visit 1 should be reported as AEs. The physical examination must be performed prior to study drug dosing during Screening Visit 1 and at Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and at Study Week 1 in the **Contingent Parallel Design**. Any significant changes in PE findings throughout the course of the study must be documented in the subject's source documents and in the eCRF.

In the event of Sponsor-approved telemedicine visits, the PE assessment will not be performed.

3.3.2.3 Vital Signs

Vital signs will include systolic and diastolic blood pressure (BP), HR, respiratory rate (RR), and weight. Height will be measured and recorded only during Screening Visit 1. Vital signs will be assessed at all study visits after at least 5 minutes of rest (seated). No other measurements or procedures should be performed during the rest period. Vital signs must be assessed prior to dosing during Screening Visit 1 and at Study Week 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and at Study Week 1 in the **Contingent Parallel Design**. When possible, vital signs should be collected prior to the 6MWT. Any clinically significant changes from Screening Visit 1 should be reported as AEs.

In the event of Sponsor-approved telemedicine visits, the vital sign assessment will not be performed.

3.3.2.4 12-Lead Electrocardiogram

A 12-lead ECG will be recorded (following at least 5 minutes of rest) during Screening Visit 1 and at study visits at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, Screening Visit 1 and at study visits at Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. No other measurements or procedures should be performed during the rest period. The ECG assessment must be performed prior to dosing during Screening Visit 1 and at Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and at Study Week 1 in the **Contingent Parallel Design.** Recordings should include lead II as a rhythm strip and contain at least 5 electrocardiographic wave (QRS) complexes. Parameters to be collected include rhythm, HR, PR interval, QT interval, QRS duration, and any clinically significant abnormalities. Any clinically significant changes from Screening Visit 1 should be reported as AEs.

In the event of Sponsor-approved telemedicine visits, the 12-lead ECG assessment will not be performed.

3.3.2.5 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed at all study visits. Blood must be drawn prior to study drug dosing during Screening Visit 1 and at Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and at Study Week 1 in the **Contingent Parallel**

Design. The results of all clinical laboratory tests performed during the Screening Period (prior to randomization) must be assessed by the Investigator to determine subject eligibility to participate prior to randomization and starting study drug.

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 subject 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.

In the event of Sponsor-approved telemedicine visits, the clinical laboratory assessments will not be performed.

3.3.2.5.1 Clinical Chemistry and Hematology

Blood will be collected to assess for treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Table 3-3 provides the values to be obtained.

Table 3-3 Clinical Chemistry and Hematology Parameters

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	

3.3.2.5.2 Pregnancy Testing

Females of childbearing potential will undergo urine (prior to the first dose of study drug) and serum pregnancy tests during Screening Visit 1, followed by a confirmatory urine pregnancy test at the Study Week 1 Visit (prior to randomization). Serum pregnancy tests will be performed at Study Weeks 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, during study visits at Study Weeks 6 & 12 or ET in the **Contingent Parallel Design**.

Pregnancy testing must be performed prior to study drug dosing during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design**, or during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**. A positive pregnancy test will result in subject withdrawal from study drug, but the subject will be encouraged to continue participation in the study and complete all study visits. See Section 9.4.2 for information related to the reporting and following of pregnancies.

In the event of Sponsor-approved telemedicine visits, serum pregnancy tests will not be performed.

3.3.2.6 Pulmonary Function Tests

Pulmonary function testing will be performed during Screening Visit 1 and at Study Weeks 1, 6, 12, 14, 19, & 25 or ET in the **Original Crossover Design**, or if applicable, at Study Weeks 1, 6, & 12 or ET in the **Contingent Parallel Design**. Pulmonary function testing should be conducted either before the 6MWT or after recovery from the 6MWT at all study visits. Pulmonary function testing should be conducted prior to study drug dosing during Screening Visit 1 and Study Weeks 1 & 14 in the **Original Crossover Design** or during Screening Visit 1 and Study Week 1 in the **Contingent Parallel Design**. If the PFTs are done both pre-bronchodilator and post-bronchodilator administration, only the post-bronchodilator values will be recorded. The following parameters will be recorded (absolute values and % predicted): FEV_1, FVC, total lung capacity (TLC), and diffusion capacity for carbon monoxide (DLCO) uncorrected for hemoglobin and lung volume; TLC and DLCO will be assessed only when clinically feasible.

In the event of Sponsor-approved telemedicine visits, PFTs will not be assessed.

3.3.2.7 At-home Spirometry

Subjects will be issued a Sponsor-provided spirometry device during Screening Visit 1 at the time of low dose inhaled treprostinil initiation for at-home capture of FEV_1 and FVC data. Subjects will be given specific instructions on how to perform the spirometry assessment. In addition, subjects will receive a copy of the Instructions for Use. Subjects will be asked to perform the spirometry assessment at home during the allowable window for each study visit. Subjects are encouraged to complete the activity ahead of their scheduled visit.

If spirometry is not performed prior to a visit, the subject should perform the spirometry assessment during the visit. Assessment of proper use and data capture should be performed by the site staff at all scheduled visits.

3.3.2.8 Computed Tomography Imaging (Required)

A CT scan should be performed prior to study drug dosing during Screening Visit 1 of the **Original Crossover Design** or during Screening Visit 1 in the **Contingent Parallel Design** to exclude disqualifying lung conditions, such as idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, diffuse parenchymal lung disease, and interstitial lung disease. A chest CT scan performed within 6 months prior to the start of Screening Visit 1 is acceptable for determining eligibility and a repeat scan is not required. A redacted CT scan report (from Screening Visit 1 or dated within 6 months prior) supporting the exclusion criterion should be provided to the Sponsor's Medical Monitor with the Pre-Baseline Review Form to confirm eligibility.

3.3.2.9 Oxygenation - Pulse Oximetry

Oxygenation via pulse oximetry will be assessed continuously prior to, during, and following each scheduled 6MWT assessment. Pulse oximetry will include the collection of saturation peripheral capillary oxygenation (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 subject's source documents and the eCRF. In addition, the lowest recorded SpO_2 (and associated HR) obtained during each 6MWT will be recorded in the subject's source documents and the eCRF.

A Sponsor-approved pulse oximeter model will be recommended and reimbursed by the Sponsor, if necessary, to maintain consistency and facilitate documentation of oxygen saturations. In the event a pulse oximeter cannot be used (ie, subject has known issues with obtaining accurate readings from a finger probe, etc), an alternative device may be used, so long as the same device is used for all subsequent testing conducted for that subject. This must be a recording oximeter that captures continuous HR and oxygenation data that can be downloaded and reviewed.

In the event of Sponsor-approved telemedicine visits, the oxygenation assessment will not be performed.

3.3.2.10 Adverse Events

Adverse events will be recorded throughout the course of the study from the time each subject signs the ICF until the time a screen failure is documented, study completion (Study Week 25 in the **Original Crossover Design**, or Study Week 12 in the **Contingent Parallel Design**), or ET. Subjects will be questioned for AEs/SAEs at each scheduled study visit and during all telephone contacts, including the Washout Period(s). Subjects will also be instructed to voluntarily report all AEs/SAEs throughout the study as warranted.

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 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 or ET.

All AEs/SAEs that occur while the subject is in the study will be recorded as instructed in this protocol. Section 9 and Appendix 15.6 provide definitions and guidelines for recording AEs/SAEs.

3.3.2.11 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 in the eCRF.

3.3.2.11.1 Supplemental Oxygen Use at Rest

The amount of supplemental oxygen (L/min) required at rest will be assessed at all scheduled visits and recorded in the subject source documents and on the concomitant medication eCRF. Supplemental oxygen therapy should not be introduced after randomization, unless there is a medical need in the clinical judgement of the Investigator; however, if supplemental oxygen therapy is started post-randomization, the flow should be consistent for all subsequent tests where oxygen is required at rest.

3.3.2.12 Weekly Telephone Contact

Weekly telephone contact is required during study drug titration (in the Screening and Treatment Periods), the Washout Period(s), and as needed thereafter to provide dosing instructions and to assess tolerance to study drug, AEs, and changes in concomitant medications. During the Washout Period(s), the telephone contact will occur mid-week between study visits.

Subjects will also be directed to call the study site coordinator or Investigator at any time to discuss study-related issues of concern (AEs, symptoms, tolerability, device issues, etc). Face-to-face interaction may replace telephone contact on the weeks where onsite study visits occur and the information can be obtained during the onsite visit. All telephone contact with subjects must be recorded in the subject's source documents and captured in the eCRF.

3.3.2.13 Telemedicine Visits

With written Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits after randomization in both the **Original Crossover Design** and the **Contingent Parallel Design**, if the conduct of an onsite study visit poses a safety risk due to the COVID-19 pandemic. The following assessments are to be completed during telemedicine visits: compliance with all study-related items (questionnaires, study drug, actigraphy, spirometry), AEs, and concomitant medications (see Section 7.4).

3.3.3 Optional Substudies

[redacted]

[redacted]

[redacted]

3.4 NUMBER OF SITES

Approximately 80 US and international sites that treat COPD subjects will be identified and recruited for this study in **Original Crossover Design**, or if applicable, approximately 100 US and international sites will be identified and recruited for this study in the **Contingent Parallel Design**.

3.5 NUMBER OF SUBJECTS

The total sample size will be approximately 136 subjects in the **Original Crossover Design**, or if applicable, approximately 314 subjects in the **Contingent Parallel Design**.

3.6 ESTIMATED STUDY DURATION

In the **Original Crossover Design**, subjects will undergo 26 weeks of treatment (over a 34-week period) as follows: at least 2 weeks of low dose (3 breaths QID) inhaled treprostinil treatment during the Screening Period (a minimum of 14 days and a maximum of 18 days if needed to

facilitate scheduling); and 24 weeks on either active or placebo, as per randomization, during Treatment Periods 1 and 2. There will be 2 Washout Periods (no treatment) for a minimum of 7 days (maximum of 14 days). Washout Period 1 (Study Week -1) will occur after the Screening Period and Washout Period 2 (Study Week 13) will occur after Treatment Period 1.

If applicable, subjects will undergo 14 weeks of treatment (over a 21-week period) in the **Contingent Parallel Design** as follows: at least 2 weeks of low dose (3 breaths QID) inhaled treprostinil treatment during the Screening Period (a minimum of 14 days and a maximum of 18 days if needed to facilitate scheduling), a Washout Period (no treatment) for a minimum of 7 days (maximum 14 days), and 12 weeks on either active or placebo, as per randomization.

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

Subjects who meet the following criteria may be included in the study:

1. Voluntarily gives informed consent to participate in the study.
2. Males and females 18 years of age and above at the time of informed consent.
   a. Females of childbearing potential (defined as less than 1 year postmenopausal and not surgically sterile) must agree to practice abstinence or use 2 highly effective methods of contraception (defined as a method of birth control that results in a less than 1% per year failure rate, such as approved hormonal contraceptives, barrier methods [condom or diaphragm] used with a spermicide, or an intrauterine device) for the duration of study treatment and for 48 hours after discontinuing study drug. Subjects must have negative pregnancy tests at Screening Visit 1 (urine [prior to the first dose of study drug] and serum) and the Baseline Visit (urine [Study Week 1]).
   b. Males with a partner of childbearing potential must agree to use a barrier method (condom) with a spermicide for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. Diagnosis of PH-COPD (WHO Group 3).
4. Clinical diagnosis of COPD per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria (2020) and documented spirometry parameters measured during Screening Visit 1 (prior to start of low dose inhaled treprostinil), as follows:
   a. FEV_1 <80% predicted
   b. FEV_1/FVC <70
5. Resting SpO_2 ≥90% during Screening Visit 1, with or without supplemental oxygen, and supplemental oxygen cannot exceed 10 L/min by any mode of delivery.
6. A 6MWD ≥100 meters during Screening Visit 1 (prior to start of low dose inhaled treprostinil).

7. Willing to undergo RHC during Screening Visit 1. An RHC performed within 12 months prior to the start of Screening Visit 1 is acceptable for determining eligibility, even if done without oxygen or vasodilator challenge, and a repeat RHC is not required. The following parameters must be documented for eligibility:
   a. PVR ≥4 Wood units
   b. Pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) of ≤15 mmHg
   c. PAPm of ≥30 mmHg
8. Must be on a stable and optimized dose of chronic COPD medications for ≥30 days prior to the start of Screening Visit 1 and remain on the same dose throughout the Screening Period.
9. Can communicate effectively with study personnel and is considered reliable, willing, and likely to be cooperative with protocol requirements, including attending all study visits, in the opinion of the Investigator.

4.2 EXCLUSION CRITERIA

Subjects who meet the following criteria are excluded from the study:

1. A diagnosis of either PAH or PH due to reasons other than COPD, including, but not limited to, chronic thromboembolic PH or acute/recent deep vein thrombosis or pulmonary embolism, untreated or inadequately treated obstructive sleep apnea, connective tissue disease (including, but not limited to, systemic sclerosis/scleroderma or systemic lupus erythematosus), sarcoidosis, human immunodeficiency virus-1 infection, and other conditions under WHO Group 1, 2, 4, and 5 classifications.
2. A confirmed diagnosis of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, diffuse parenchymal lung disease, or interstitial lung disease, based on chest CT imaging during Screening Visit 1. A chest CT performed within 6 months prior to the start of Screening Visit 1 is acceptable for determining eligibility and a repeat assessment is not required. A redacted CT scan report (from Screening Visit 1 or dated within 6 months prior) should be provided to the Sponsor's Medical Monitor with the Pre-Baseline Review Form to confirm eligibility.
3. Received any Food and Drug Administration (FDA)-approved medication for the treatment of PAH (ie, prostacyclin, prostacyclin receptor agonist, endothelin receptor antagonist [ERA], phosphodiesterase type 5 inhibitor [PDE5-I], or soluble guanylate cyclase [sGC] stimulator) at Screening Visit 1 and thereafter, except if received for acute vasoreactivity testing.
4. Previous diagnosis of homozygous alpha-1 antitrypsin deficiency.
5. Any prior intolerance to inhaled prostanoid therapy.
6. Inability to tolerate low dose inhaled treprostinil and/or follow dosing regimen during the Screening Period (pre-randomization).
7. Unwilling or unable to use Sponsor-provided devices (actigraph, spirometer, or smart device).

8. Evidence of clinically significant left-sided heart disease (including, but not limited to, left ventricular ejection fraction <40%, left ventricular hypertrophy) or clinically significant cardiologic conditions, such as congestive heart failure, coronary artery disease, or valvular heart disease. NOTE: Subjects with abnormal left ventricular function attributable to the effects of right ventricular overload will not be excluded, but a discussion with and approval by the Sponsor's Medical Monitor is required.
9. Any exacerbation of COPD (including hospitalization or outpatient therapy) or active pulmonary or upper respiratory infection from 30 days prior to start of Screening Visit 1 through the Baseline Visit. This is defined as worsening of respiratory symptoms that required treatment with corticosteroids and/or antibiotics.
10. Initiation of pulmonary rehabilitation within 12 weeks prior to start of Screening Visit 1 or, in the opinion of the Investigator, pulmonary rehabilitation is likely to be needed during the Treatment Period.
11. Any form of congenital heart disease (repaired or unrepaired) other than a patent foramen ovale.
12. Any musculoskeletal disorder (ie, severe arthritis of the lower limbs which limits ambulation, recent hip or knee joint replacement, artificial leg) or any other condition that would likely be the primary limitation to ambulation.
13. Use of any other investigational drug or device within 30 days prior to the start of Screening Visit 1.
14. Any other clinically significant illness or abnormal laboratory value(s) measured during the Screening Period that, in the opinion of the Investigator, might adversely affect the interpretation of the study data or safety of the subject.

4.3 PRESCRIBED THERAPY

Subjects must not be receiving any FDA-approved medication to treat PAH (ie, prostacyclin, prostacyclin receptor agonist, ERA, PDE5-I, or sGC stimulator) at Screening Visit 1 and thereafter, except if received for acute vasoreactivity testing.

Subjects on a chronic medication for COPD should be on a stable and optimized dose for ≥30 days prior to the start of Screening Visit 1 and remain on the same dose throughout the Screening Period. After randomization, subjects should remain on a stable dose until the end of the study, as much as feasible. When applicable, it is recommended that study drug be administered after concomitant bronchodilators.

Subjects must not be participating in any other investigational study involving an investigational drug or device within 30 days prior to start of Screening Visit 1 or during the study.

Subjects may not initiate pulmonary rehabilitation within 12 weeks prior to the start of Screening Visit 1 through the end of the study.

All concomitant medications taken during the conduct of the study, including supplemental oxygen, and those taken for AEs or other medical events, should be recorded in the subject's source documents and transcribed into the eCRF. The flow rate of supplemental oxygen should be recorded as outlined in Section 3.3.2.11.1.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

In the **Original Crossover Design**, which is a crossover study, approximately 136 subjects will receive inhaled treprostinil and placebo. If applicable, in the **Contingent Parallel Design**, which is a parallel study (approximately 314 subjects), at least 157 subjects will receive inhaled treprostinil and another 157 subjects will receive placebo.

5.2 RANDOMIZATION

Prior to randomization, at Screening Visit 2 (Study Week -2), site personnel should complete the Pre-Baseline Review Form, confirm study drug tolerability and compliance during the Screening Period, and request the Sponsor's Medical Monitor review subject eligibility. Randomization will not be possible until the Pre-Baseline Review Form (and supporting documentation) is complete and the Sponsor's Medical Monitor confirms subject eligibility. Subjects who are intolerant of therapy (as determined by the Investigator), unable to follow the dosing regimen, or noncompliant with actigraphy, at-home spirometry, or smart device use during the Screening Period will be ineligible for randomization and deemed screen failures. Subjects may be re-screened (see Section 3.1).

An Interactive Response Technology (IRT) ([redacted]) will be utilized for the central randomization procedure. Sites will access the IRT and conduct the randomization steps if the subject is approved for the study.

In the **Original Crossover Design**, subjects will be randomized to receive treatment with either inhaled treprostinil (6 mcg/breath, target of 12 breaths QID or the maximum tolerated dose) or placebo in Treatment Period 1 (at Study Week 1), followed by a crossover to the other treatment

in Treatment Period 2 (at Study Week 14). There will be a Washout Period (no treatment; Study Week 13) for a minimum of 7 days (maximum of 14 days) between Treatment Periods 1 and 2. If the Sponsor adapts the study to the **Contingent Parallel Design**, any subject in Treatment Period 2 will be asked to return to the site as soon as possible to complete an ET Visit.

In the **Contingent Parallel Design** (if applicable), subjects will be randomized to receive treatment with either inhaled treprostinil (6 mcg/breath, target of 12 breaths QID or the maximum tolerated dose) or placebo at Study Week 1.

5.3 BLINDING

The subjects, Investigators, study site personnel, and Sponsor (United Therapeutics Corp. [UTC] and its designee, Lung Biotechnology PBC), with the exception of select UTC Pharmacovigilance and Drug Supply staff, will be blinded to the treatment assignment of the subject, unless unblinding is required for safety review or regulatory reporting.

The site staff must never be unblinded to the treatment assignment of participating subjects, unless deemed medically necessary (see Section 6.2).

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 the Tyvaso Inhalation System, which emits a dose of approximately 6 mcg per breath. Placebo will be provided as an identical solution for inhalation using the same Tyvaso Inhalation System. Subjects will receive study drug (inhaled treprostinil or placebo) via the Tyvaso Inhalation System and will be trained on use of the Tyvaso Inhalation System at Screening Visit 1. In addition, subjects will receive a copy of the Tyvaso Inhalation System Instructions for Use. The first dose of study drug (3 breaths, 18 mcg) will be inhaled at the study site, followed by at least a 1-hour observation period.

Once informed consent has been signed, all entry criteria have been met (including Sponsor Medical Monitor Approval), and the randomized treatment assignment confirmed, study drug doses should be maximized throughout the study and dose escalations (additional 1 breath QID) can occur approximately every 3 days with a target dosing regimen of 12 breaths (72 mcg) QID

or the maximum tolerated dose. Table 6-1 provides an example of dose escalations that can be followed.

Table 6-1 Sample Inhaled Treprostinil Dose Escalation Table

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

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

The above dosing schedule is recommended as a guide only. The Investigator may accelerate or decelerate the dosing titration schedule on an individual subject basis, considering subject safety, tolerability, and functional improvement.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site staff. Telephone calls between the site staff and subject should occur prior to each dose adjustment, or at least weekly during titration (until 12 breaths QID or the maximum tolerated dose is achieved), and as needed thereafter to provide dosing instructions and to assess tolerance to study drug, AEs, and changes in concomitant medications. If subjects are prescribed bronchodilators, study drug should be taken after.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

The subjects, Investigators, study site personnel, and Sponsor (UTC and its designee, Lung Biotechnology PBC) are blinded to the treatment assignments of all subjects throughout the study. Exceptions are the UTC Pharmacovigilance and Drug Supply staff (and their designated third-party vendors), who are unblinded for packaging and labeling of study drug and for safety reporting per local, national, and international regulations. If unblinding of a subject's treatment assignment is necessary for the safety of a subject, the Investigator (or Sponsor's Medical

Monitor) would perform an unblinding of a subject's treatment assignment through the IRT. Appropriate communication should take place between the site and the Sponsor before accessing the IRT to enable the unblinding.

6.3 COMPLIANCE

At each study visit, all study drug returned by the subject (used and unused) will be collected and new study drug will be dispensed as needed. The appropriate study personnel must document the number of used and unused ampoules. To accommodate Sponsor-approved telemedicine visits, study drug and device supplies will be allowed to be shipped directly to the subject.

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each study visit, the subject will be asked whether they have been compliant with dosing instructions. If it is determined that a subject is noncompliant with study drug, the site personnel must re-educate the subject on proper dosing compliance and its importance. Continued noncompliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor's Medical Monitor or other Sponsor representative.

7 EXPERIMENTAL PROCEDURES

The allowable window for each study visit will be ±3 days; however, where specified, the minimum Treatment or Washout Period must be adhered. Refer to Section 3.2 for the Overall Schedule of Times and Events.

7.1 SCREENING PERIOD

7.1.1 Screening Visit 1 (Study Weeks -9 to -3)

All procedures may be conducted over a 6-week period to facilitate scheduling. The following assessments for Screening Visit 1 are required prior to dosing with study drug:

- Informed consent
- Demographics
- Medical history, including PH-COPD history
- PE
- Vital signs: height, weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period
- 12-lead ECG (following at least 5 minutes of rest)

- Blood draws for NT-proBNP and clinical laboratory parameters
- [redacted]
- Urine (prior to the first dose of study drug) and serum pregnancy tests for females of childbearing potential
- 6MWT and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following the 6MWT
- PFTs (performed either before the 6MWT or after recovering from the 6MWT, if applicable)
- Chest CT scan; if performed within 6 months prior to the start of Screening Visit 1 a repeat assessment is not required. A redacted CT scan report should be provided to the Sponsor's Medical Monitor with the Pre-Baseline Review Form to confirm eligibility.
- Review inclusion/exclusion criteria
- RHC; an RHC obtained within 12 months prior to the start of Screening Visit 1 is acceptable for determining eligibility, even if done without oxygen or vasodilator challenge, and a repeat RHC is not required.

If all study eligibility criteria are met, dosing instructions and Tyvaso Inhalation device training will occur, followed by administration of study drug. The subject must remain at the study site for at least 1 hour after the first dose of study drug for observation. The following assessments should be completed after dosing:

- Assess for AEs
- Assess for changes in concomitant medications
- Issue the Sponsor-provided actigraphy, spirometry, and smart devices and provide training on use of the devices
- Subjects will be called weekly during the Screening Period and directed to call the study site coordinator or Investigator at any time to discuss study-related issues of concern (AEs, symptoms, tolerability, device issues, etc)

Re-screening: Subjects may be re-screened. The study-specific RHC performed during Screening Visit 1 is valid for up to 12 months and should not be repeated if the subject is being re-screened unless written approval is first obtained from the Sponsor's Medical Monitor.

7.1.2 Screening Visit 2 (Study Week -2)

- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period

- Blood draws for NT-proBNP and clinical laboratory parameters
- Collect study drug from subject and complete drug/device accountability
- Assess for AEs
- Assess for changes in concomitant medications
- Confirm study drug tolerability and compliance during the Screening Period
- Review inclusion/exclusion criteria and confirm study eligibility
- Complete the Pre-Baseline Review Form for Sponsor's Medical Monitor review and approval if subject tolerates drug and meets all other eligibility criteria
- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Subjects will be directed to call the study site coordinator or Investigator at any time to discuss study-related issues of concern (AEs, symptoms, tolerability, etc)

7.2 WASHOUT PERIODS

7.2.1 (Study Week -1 and Study Week 13)

At the end of Screening Visit 2 (**Original Crossover Design** and **Contingent Parallel Design**) and Study Week 12 (**Original Crossover Design**), all subjects will enter a 7-day minimum (14 days maximum) Washout Period.

Subjects will be called mid-week following discharge from the site and directed to call the study site coordinator or Investigator at any time to discuss study-related issues of concern (AEs, concomitant medications, symptoms, tolerability, etc).

7.3 TREATMENT PERIODS

7.3.1 Study Week 1 Visit (Baseline Visit)

The following baseline assessments must be performed prior to the first dose of study drug at the Study Week 1 Visit:

- QOL questionnaires: SGRQ and UCSD SOBQ
- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period
- 12-lead ECG (following at least 5 minutes of rest)
- Blood draws for clinical laboratory parameters and NT-proBNP (NT-proBNP sample must be drawn prior to 6MWT)
- [redacted]

- [redacted]
- [redacted]
- Reconfirm inclusion/exclusion criteria
- Confirm Sponsor's Medical Monitor approval to randomize subject
- Urine pregnancy test for females of childbearing potential
- Randomization using IRT
- PFTs (must be done after randomization either before the 6MWT or after recovery from the baseline 6MWT)
- 6MWT (conducted post randomization; following at least 10 minutes of seated rest) and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following 6MWT
- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Collect PGA and provide training on at-home completion of the PGA

After the above assessments are completed, the following should be conducted:

- Provide and administer study drug, including dosing instructions
- Assess for AEs
- Assess for changes in concomitant medications
- Provide paper QOL questionnaires and training on at-home completion in the event telemedicine visits are needed
- Weekly telephone contact

7.3.2 Study Weeks 6 and 19 Visits

The following assessments are to be completed during Study Weeks 6 & 19 in the **Original Crossover Design**, or if applicable, Study Week 6 in the **Contingent Parallel Design**:

- QOL questionnaires: SGRQ and UCSD SOBQ
- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period
- 12-lead ECG (following at least 5 minutes of rest)
- Blood draws for clinical laboratory parameters and NT-proBNP (NT-proBNP sample must be drawn prior to 6MWT)

- Serum pregnancy test for females of childbearing potential
- Administer study drug at the study site
- 6MWT (to be conducted between 10 to 60 minutes after study drug administration and following at least 10 minutes of seated rest) and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following the 6MWT
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Confirm proper use and capture of PGA data
- Provide study drug and assess drug/device accountability
- Assess for AEs
- Assess for changes in concomitant medications
- Weekly telephone contact

7.3.3 Study Week 14 Visit

The following assessments are to be completed prior to the first dose of study drug during Study Week 14 in the **Original Crossover Design** only:

- QOL questionnaires: SGRQ and UCSD SOBQ
- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period
- 12-lead ECG (following at least 5 minutes of rest)
- Blood draws for clinical laboratory parameters and NT-proBNP (NT-proBNP sample must be drawn prior to 6MWT)
- Serum pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- [redacted]
- 6MWT (following at least 10 minutes of seated rest) and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following the 6MWT
- PFTs (performed before the 6MWT or after recovery from the 6MWT)

- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Confirm proper use and capture of PGA data

After the above assessments are completed, the following should be performed:

- Provide and administer study drug, including dosing instructions
- Assess for AEs
- Assess for changes in concomitant medications
- Weekly telephone contact

7.3.4 Study Weeks 12 and 25 Visits

The following assessments are to be completed during Study Weeks 12 & 25 in the **Original Crossover Design** or, if applicable, Study Week 12 in the **Contingent Parallel Design**:

- QOL questionnaires: SGRQ and UCSD SOBQ
- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period
- 12-lead ECG (following at least 5 minutes of rest)
- Blood draws for clinical laboratory parameters and NT-proBNP (NT-proBNP sample must be drawn prior to 6MWT)
- Serum pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- [redacted]
- Administer study drug at the study site
- 6MWT (conducted between 10 to 60 minutes after study drug administration and following at least 10 minutes of seated rest) and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following the 6MWT
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Confirm proper use and capture of PGA data
- Provide study drug and assess drug/device accountability

- Assess for AEs
- Assess for changes in concomitant medications
- Weekly telephone contact

At the end of Study Week 25 in the **Original Crossover Design**, or if applicable, Study Week 12 in the **Contingent Parallel Design**, subjects will be terminated from the study. Subjects who meet all eligibility criteria will be offered enrollment in the open-label extension study, RIN-PH-305.

7.4 TELEMEDICINE VISITS

With written Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits after randomization in both the **Original Crossover Design** and the **Contingent Parallel Design**, if the conduct of an onsite study visit poses a safety risk due to the COVID-19 pandemic. The following assessments will be performed during the telemedicine visits:

- Confirm completion of paper QOL questionnaires: SGRQ and UCSD SOBQ
- Confirm proper use and capture of actigraphy data
- Confirm proper use and capture of spirometry data
- Confirm proper use and capture of PGA data
- Confirm receipt of study drug resupply and dosing of study drug
- Assess for AEs
- Assess for changes in concomitant medications

7.5 EARLY TERMINATION VISIT

If the subject permanently discontinues study drug prior to Study Week 25 in the **Original Crossover Design**, or if applicable, Study Week 12 in the **Contingent Parallel Design**, for any reason, the subject should be encouraged to remain in the study and complete all visits up to and including the ET Visit.

If a decision is made to terminate a subject early from the study, the following assessments should be conducted as soon as possible and prior to study drug discontinuation, if possible:

- QOL questionnaires: SGRQ and UCSD SOBQ
- PE
- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest and collected prior to 6MWT); no other measurements or procedures should be performed during the rest period

- 12-lead ECG (following at least 5 minutes of rest)
- Blood draws for clinical laboratory parameters and NT-proBNP (NT-proBNP sample must be drawn prior to 6MWT)
- Serum pregnancy test for females of childbearing potential
- [redacted]
- [redacted]
- [redacted]
- 6MWT (if possible, to be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of seated rest) and, if applicable, documentation of supplemental oxygen requirement
- Pulse oximetry (performed continuously prior to, during, and following the 6MWT)
- Borg dyspnea score immediately following the 6MWT
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Confirm capture of actigraphy data
- Confirm capture of spirometry data
- Confirm capture of PGA data
- Verify study drug/device accountability
- Assess for AEs
- Assess for changes in concomitant medications

7.6 ACCESS TO OPEN-LABEL STUDY

Subjects who meet all eligibility criteria will be offered enrollment in the open-label extension study, RIN-PH-305.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

Investigators and site staff should encourage subjects to continue participation in the study and complete all study procedures and study visits as indicated by the study protocol, unless subjects provide written withdrawal of consent from the study.

8.1.1 Criteria for Withdrawal from Study Drug

Subject discontinuation from study drug does not mean discontinuation from the study. Subjects may voluntarily withdraw from study drug for any reason or the study drug may be withdrawn by the Investigator to protect subject safety. If a subject is withdrawn from study drug, the subject will be encouraged to actively continue to return for all study visits per the study protocol

and the Investigator will continue all reasonable efforts to obtain subject data. The primary reason for withdrawal from study drug should be documented in the subject's eCRF. If 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 follow up, or for 30 days if the AE extends beyond the final visit. If a subject discontinues study drug prematurely due to an SAE, the subject should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 30 days after completion of the final visit.

A positive pregnancy test will result in subject withdrawal from study drug, but the subject will be encouraged to continue participation in the study and complete all study visits. See Section 9.4.2 for information related to the reporting and following of pregnancies.

8.1.2 Criteria for Subject Withdrawal from Study

Subjects may voluntarily withdraw from the study at any time for any reason after completing a formal and written withdrawal of consent. A withdrawal of consent would preclude data collection regarding that subject after the date that the withdrawal of consent was documented. The date that consent was withdrawn should be documented in the subject's eCRF.

8.2 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of 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 unanticipated in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.3 CRITERIA FOR DISCONTINUING A SITE

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

- The Investigator elects to discontinue the study.
- The Sponsor elects to discontinue the study at the site.
- Applicable regulations are not observed.
- The protocol is repeatedly violated or critical violations are documented.
- Changes in personnel or facilities adversely affect performance of the study.

9 ADVERSE EVENT REPORTING

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

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.1.2 Serious Adverse Event

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

- Death
- Life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require medical/surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or abuse.

Life-threatening means that the subject was at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death.

9.2 DOCUMENTATION OF ADVERSE EVENTS

All AEs will be documented from the time of informed consent until the time screen failure is documented, study completion, or early termination. An AE 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 15.6 for definitions). Where possible, AEs should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

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 should be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 30 days after completion of the final visit.

Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or causality of an AE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The applicable eCRF pages should be updated with any new or additional information, as appropriate.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

9.4.1 Serious Adverse Event Reporting

Sites should enter all available initial and follow-up SAE information into the eCRF (primary method) within 24 hours of awareness of the information, regardless of causality or expectedness. The SAE information will be transmitted directly from the eCRF into the safety database (Argus). If the site is unable to enter the SAE information into the eCRF within 24 hours of awareness, the alternative method is to email a paper SAE Report Form to [redacted] or fax it to [redacted].

Any information submitted on a paper SAE Report Form must also be entered into the eCRF by the study site as soon as possible thereafter. Any subject source documents related to the SAE (eg, hospital discharge summary, treatment records, death certificate, diagnostic test results) should be emailed to [redacted]. The Investigator or Sponsor (if appropriate) must also notify their Institutional Review Board (IRB), Independent Ethics Committee (IEC), and/or other local equivalent body of the reported SAE, including any follow-up information. Copies of each report and documentation of IEC/IRB/local equivalent body notification and receipt will be kept in the Investigator study file.

9.4.2 Pregnancy Reporting

Both female and male subjects must be instructed to contact the Investigator immediately if they suspect they or their partner became pregnant while participating in this study. Any pregnancy that occurs during the study must be reported to the Sponsor via email [redacted] or fax [redacted] using the Pregnancy Notification and Outcome Form within 24 hours of awareness. All pregnancies, including those of a male subject's female partner, must be followed until outcome. A pregnancy is not an AE/SAE. If there is an abnormal pregnancy outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring, the pregnancy outcome becomes an AE/SAE.

9.5 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 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

This section briefly describes the planned statistical analyses. A complete description of the methodology will be specified in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

10.1 DATA PROCESSING

The study eCRF is the primary data collection instrument for the study. All data requested on the eCRF must be recorded following the eCRF completion guidelines to be provided to site personnel. Subject data will be entered in the eCRF for all subjects who sign an ICF until study completion or study discontinuation by appropriate site staff. Data recorded in the eCRF should be consistent with source documents. A representative from the Sponsor will verify eCRF data fields against source documentation per the established monitoring plan.

All data transmitted from the site will be reviewed by the Sponsor and data clarification requests may be generated in the eCRF, 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 their approval of the data. The Investigator will be required to re-sign an eCRF if changes are made by the site after the Investigator initially signs the eCRF. The clinical database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

Additional data resulting from actigraphy, spirometry, and PGA will be transmitted to the Sponsor from the respective vendors during the study and at study completion. These data will be reviewed by the Sponsor accordingly, but will not be recorded in the eCRF. These data will be merged into the clinical database after completion of the study.

10.2 SAMPLE SIZE

This is an adaptive design study that will be initiated as a crossover study (the **Original Crossover Design)**. However, due to the uncertainty of clinical benefit with inhaled treprostinil exposure in PH-COPD subjects and the ongoing COVID-19 pandemic, there is a possibility of treatment discontinuations and/or missing data due to COVID-19 impeding onsite visits, which may render estimates for efficacy outcomes inefficient or biased, thus an automatic switch to the **Contingent Parallel Design** or an alternative primary endpoint that has been incorporated in this study protocol. The protocol specifies the algorithm to seamlessly transition to a parallel-group design (**Contingent Parallel Design**) if the degree of missing data subsequent to subject treatment crossover is not tolerable for primary analysis.

Similarly, this protocol specifies the algorithm to switch the primary endpoints to measurements conducted remotely if the COVID-19 pandemic prevents onsite visits and data collection for the intended primary endpoint data. Evaluations of missing data will be performed in a blinded fashion at the conclusion of the study, irrespective of actual efficacy outcomes and any information regarding efficacy outcomes prior to crossover and, as such, will not impact the Type I error rate (FDA Guidance 2019). Section 10.2.1 presents the adaptation procedures to be employed for this protocol.

The **Original Crossover Design** is a 2x2 crossover study designed to have 90% power to detect a placebo-corrected mean change from baseline difference of 30 meters, assuming that the standard deviation of differences is 85 meters and using a 2-group t-test with a 0.01 two-sided significance level, with a sample size of 124 subjects (62 in each sequence group). To account for a discontinuation rate of approximately 10%, the total sample size will be approximately 136 subjects.

Based on published data using actigraphy as an outcome measure in studies conducted in the pulmonary hypertension population (Gonzalez-Saiz 2018; Nathan 2020), reasonable statistical power (80%; 2-sided alpha of 0.05) can be assumed for approximately 90 evaluable subjects when the observed improvement is in excess of 6%-8% for overall activity or 20-25% or greater for moderate to vigorous activity. Nathan (2019) provides that the clinically meaningful difference observed in their study was 5% to 10% for overall activity and 20% for MVPA, with a clinically meaningful difference range in studies of COPD patients from 11% to 29%.

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

10.2.1 Adaptive Design Procedures

This adaptive study will be initiated as an **Original Crossover Design**. Two separate missing data checks will occur and will result in study design adjustment decisions. The following adaptation strategies will be used:

Adaptation 1:

At approximately 75% of subjects randomized, a blinded interim analysis will be performed to assess the extent of missing primary efficacy endpoint data at the end of Treatment Period 2 (Study Week 25). The outcome of the analysis will inform a decision for the study to continue as the **Original Crossover Design** or switch to the **Contingent Parallel Design** as follows:

- If data presence ≥85% for 6MWD or actigraphy data at the end of Treatment Period 2 (Study Week 25), the study will continue as planned under the **Original Crossover Design**.
- If data presence <85% for both 6MWD and actigraphy data at the end of Treatment Period 2 (Study Week 25), the study will switch to the **Contingent Parallel Design**.

Adaptation 1 will assess the amount of missing exercise ability data due to subject dropout or otherwise lack of measurement (regardless of onsite or remote) and the outcome will be whether study continues to completion as the **Original Crossover Design** or the **Contingent Parallel Design**.

Adaptation 2:

Will assess the amount of missing exercise ability data potentially due to the COVID-19 pandemic interfering with onsite measurements. At the conclusion of the study, a blinded analysis will be performed to assess the extent of missing primary efficacy endpoint data (ie, 6MWD data). If the absence of 6MWD data in the Treatment Period of the study, combined across subjects, treatment periods, and key visits (Baseline and Study Week 12) to be used for the final primary endpoint analysis would likely lead to an underpowered study or yield indeterminate results, a contingent primary endpoint will be used for the final primary endpoint analysis. Such a contingency may include an imputation of missing 6MWD data from actigraphy measurements or the use of actigraphy measurements alone rather than 6MWD for the primary endpoint analysis.

This adaptation intends that the 6MWD is to be used as the primary efficacy endpoint for this study, except in the case where onsite measurements for the 6MWD are not reasonably available and will occur regardless of Adaptation 1 (ie, for either the **Original Crossover Design** or the **Contingent Parallel Design**). The contingent primary endpoint definition and analysis strategy will be specified a priori with details fully documented in the SAP prior to the unblinding of the study.

As outlined in Section 8.2, the Sponsor reserves the right to discontinue the study for any reason, at any time.

10.3 ANALYSIS PLAN

Statistical analyses will be performed using 2-sided tests. A 0.05 significance level will be used in all tests of treatment differences. In addition, for labeling purposes only, the experiment-wise Type I error will be controlled to a maximum of 5%. A gatekeeper strategy may be employed such that any secondary endpoints or subset analyses will be considered for statistical significance only if the primary endpoint is statistically significant. The Type I family-wise error rate will be controlled at the 0.05 level of significance.

Data will be summarized by treatment group (and by visit when applicable). For parameters measured at baseline, the outcome variables of interest are the changes from baseline.

Summary statistics will include the mean, N, standard deviation, median, minimum, maximum, the 25th and 75th percentile values for continuous variables, and frequencies and percentages for categorical variables.

The SAP will specify the details of the models to be used for the efficacy, safety, and exploratory analyses. All statistical analyses will be performed by the Sponsor's biostatistics department personnel (or appropriate designees) using SAS®, Version 9.3 or higher or other validated software.

The Full Analysis Population will be defined as all subjects randomized into the study who receive at least 1 dose of study drug; all subjects will be counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses will be performed on this population, unless otherwise specified.

The Safety Population will be defined as all subjects enrolled into the study who receive at least 1 dose of study drug; all Safety Population subjects will be counted in the group corresponding to the study drug actually received, regardless of randomized assignment. All safety analyses will be performed on this Safety Population, unless otherwise specified.

10.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in 6MWD measured at peak exposure (defined as 10 to 60 minutes after dosing) after 12 weeks of study drug treatment. The primary endpoint analysis will evaluate the difference in baseline-corrected 6MWDs between active and placebo conditions. The primary endpoint analysis will test the hypothesis of an improvement in baseline-corrected 6MWDs for active compared to placebo conditions as administered to subjects with PH-COPD. The primary null hypothesis to be tested is that there are no differences in the baseline-corrected 6MWDs between active and placebo conditions.

A mixed-effect model repeated measure will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated across the 12-week conditions between 2 treatment groups and the test of the Week 12 treatment effect will be produced using contrasts.

Sensitivity analyses to support the primary endpoint analysis will be conducted to examine robustness of results under various assumptions underlying the analysis (eg, normality, effects of dropout).

10.3.2 Alternate Primary Efficacy Endpoint

The analysis strategy will be specified a priori with details fully documented in the SAP prior to the unblinding of the study.

10.3.3 Secondary Efficacy Endpoint(s)

The effect of inhaled treprostinil after 12 weeks of treatment will be formally tested on the following secondary efficacy endpoints:

1. Change in MVPA as measured by actigraphy
2. Change in overall activity as measured by actigraphy
3. Change in Borg dyspnea score from baseline
4. Change in 6MWD/Borg dyspnea composite score from baseline
5. Change in QOL from baseline as measured by SGRQ and UCSD SOBQ

6. Change in plasma concentration of NT-proBNP from baseline
7. Change in PGA

Hypothesis testing of secondary efficacy endpoints will be conducted using a gatekeeper strategy, such that any secondary endpoints will be considered for statistical significance only if the primary endpoint is statistically significant. Under closed testing procedures, the Type I family-wise error rate will be controlled at the 0.05 level of significance. The SAP will detail the specific analyses and methods for testing of secondary efficacy endpoints.

10.3.4 Safety Analyses

The safety of inhaled treprostinil compared to placebo will be evaluated on the following parameters: AEs, clinical laboratory assessments, ECGs, PE findings, oxygenation, PFTs, vital sign measurements, and at-home spirometry.

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

Data collected prior to dosing will serve as baseline values for the evaluation of data collected during the Treatment Period. Summary statistics will be calculated for measured values and changes from baseline values. Treatment-emergent changes in clinical laboratory evaluations, ECGs, oxygenation, PFTs, at-home spirometry, and vital sign measurements will be summarized by treatment group. No inferential analyses are planned on these safety endpoints.

10.3.5 Exploratory Analyses

[redacted]

[redacted]

10.4 INTERIM ANALYSIS

An interim analysis is planned in a blinded fashion, at approximately 75% of subjects randomized, to assess the extent of missing primary efficacy endpoint data at the end of Treatment Period 2. The outcome of this analysis will inform a decision for the study to continue with the **Original Crossover Design** or switch to the **Contingent Parallel Design**. Full details of the adaptation procedures are specified in Section 10.2.1.

A single interim efficacy analysis will be conducted when at least 75% of the subjects (ie, ~100 subjects) have completed the 26-week Treatment Period, data are available for both Treatment Period 1 and Period 2 6MWD evaluations, and if the expected time to randomize the final (136th) subject is greater than 3 months. The expected time to randomize will be based on the average recruitment rate for the prior 6 months. This plan will allow early stopping for convincing evidence of benefit if recruitment is slow. A non-binding futility analysis will be conducted at the same time. The results of these analyses will be provided to the independent Data Safety Monitoring Committee (DSMC) by the independent external consultant for their review and recommendation. The DSMC Charter and SAP will contain the approach for projecting recruitment, as well as formal criteria for the interim analyses for efficacy and futility. The Sponsor will remain fully blinded throughout this process.

10.5 OTHER ANALYSES

Other analyses may be conducted based on available study data. Details for any other planned statistical analyses will be specified in the SAP.

10.6 DATA LISTINGS AND SUMMARIES

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

10.7 DATA SAFETY MONITORING COMMITTEE

A DSMC will be established for the study, including physicians knowledgeable in the treatment of PH-COPD. Throughout the course of the study, the DSMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DSMC charter.

The DSMC will be unblinded to individual subject treatment allocation during the review process. All analyses will be prepared by an independent external consultant and reviewed only by the DSMC, as defined in the DSMC charter. The Sponsor will only have access to blinded study data during this process.

11 PACKAGING AND FORMULATION

11.1 STUDY SUPPLIES

11.1.1 Actigraphy, Spirometry, and Smart Devices

The Sponsor will supply sufficient quantities of actigraphy, spirometry, and smart devices to begin enrollment in the study. The devices will be supplied using standard packaging labeled with the study number, accompanied by the Instructions for Use. Site staff will dispense these devices to eligible subjects during Screening Visit 1 at the time of low dose inhaled treprostinil initiation.

If a device is defective or suspected to be defective and the issue cannot be resolved via troubleshooting, the site should complete the Product Complaint Form provided in the Study Procedures Manual, return the form to the Sponsor within 24 hours, and follow any additional instructions provided by the Sponsor. As indicated in the Study Procedures Manual, a new device will be issued to the subject.

11.2 CONTENTS OF STUDY DRUG

11.2.1 Study Drug (Active and Placebo)

The Sponsor will supply active study drug (treprostinil inhalation solution, 0.6 mg/mL) and placebo study drug as a clear liquid in 2.9-mL ampoules. Each ampoule will provide for a single day of treatment across the QID dosing. The ampoules will be packaged in groups of 4, sealed in aluminum foil pouches. During Screening Visit 1, subjects will be supplied cartons containing 5 pouches per carton to last the 2-week assessment of tolerability and follow the QID dosing regimen in the Screening Period. After randomization, subjects will be supplied cartons containing 12 pouches per carton.

If a study drug is believed to be suspect by site staff or a subject, the site should complete the Product Complaint Form provided in the Study Procedures Manual, return the form to the Sponsor within 24 hours, and follow any additional instructions provided by the Sponsor.

11.2.2 Study Inhalation Device

The Sponsor will supply the Tyvaso Inhalation System and accessories to the site in standard packaging labeled with the study number. The Tyvaso Inhalation System will also be provided with the Tyvaso Inhalation System Instructions for Use.

Subjects will receive 2 Tyvaso Inhalation Systems during Screening Visit 1 at the time of low dose inhaled treprostinil initiation. In addition, the subjects will be provided with the appropriate number of plastic device accessories at each study visit. Damaged devices should be replaced as needed during the study.

If a device is defective or suspected to be defective and the issue cannot be resolved via troubleshooting, the site should complete the Product Complaint Form provided in the Study Procedures Manual, return the form to the Sponsor within 24 hours, and follow any additional instructions provided by the Sponsor. As indicated in the Study Procedures Manual, a new device will be issued to the subject.

The Investigator or designee will give subjects further instructions regarding the return of the Tyvaso Inhalation Systems at the completion of this study.

11.3 LABELING

11.3.1 Study Drug (Active and Placebo)

The foil pouch and the outer carton will each be labeled with the same information and sent to the study site. At a minimum, the study drug outer packaging (pouch and carton) will be labeled to clearly display 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).

11.3.2 Study Inhalation Device

The Tyvaso Inhalation System and accessories and will be supplied using standard packaging labeled with the study number.

11.4 STORAGE AND HANDLING OF STUDY DRUG

All study drug will be stored at room temperature ~25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Study drug should not be frozen, refrigerated, or exposed to heat.

The ampoules must be kept in the foil pouch to protect from light. Subjects should be instructed that once the foil pouch is opened, the study drug should be used within 7 days. See the study drug label for information on use and storage of the product.

Study drug will be stored at the site in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access should be strictly limited to the Investigators and their designees. Investigators or their designees may not provide study drug to any individual not participating in this protocol.

11.5 SUPPLY AND RETURN OF STUDY DRUG AND DEVICES

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At each study visit, all study drug previously dispensed to a subject should be returned to the study site, including all used and unused ampoules.

In the event of Sponsor-approved telemedicine visits, study drug and device accessories may be sent to subjects via mail.

Subjects should return all Sponsor-provided devices and any remaining study drug to the study site at the end of the study (withdrawal, discontinuation, termination, or completion).

In the event of Sponsor-approved telemedicine visits, the Sponsor-provided devices and study drug may be returned to the study site via mail.

11.6 DRUG AND DEVICE ACCOUNTABILITY

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

At each applicable visit, site personnel will:

- Collect and document all study drug/device returned by the subject (both used and unused).
- Assess study drug compliance using the dosing instructions given to the subject since the previous study visit and the amount of study drug returned.

- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

Once a Sponsor's representative confirms drug/device accountability for a completed subject, used and unused study drug can either be destroyed onsite locally and a destruction certification placed in the subject's file, or alternately, the study drug can be shipped to the Sponsor-designated location for destruction.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 US FDA OR APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with International Council for Harmonisation (ICH), Good Clinical Practices (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/IECs that require it. Any additional national reporting requirements specified by the applicable regulations, regulatory authorities, or IRB/IEC 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 their 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/IEC-approved ICF prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject and the original will be retained in the study site records.

The subject should also be informed that if they wish to withdraw from the study any time, a written withdrawal of consent will be required.

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/IEC and provide the Sponsor or designee with a copy of the approval letter. The IRB/IEC must also review and approve the study site ICF and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject

recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor or designee for review before submission to the IRB/IEC prior to the start of the study.

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

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/IECs 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/IEC standard procedures. Additional updates will also be provided in accordance with the IRB/IEC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical study, the following documents will be provided to the site: Investigator's Brochure, protocol, ICF, budget agreement, and eCRF.

The site will be required to provide the following documents to UTC's designee (Lung Biotechnology PBC) prior to study start: signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/IEC Composition and Roster, IRB/IEC 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. UTC, Lung Biotechnology PBC, the FDA or other regulatory bodies, and the IRB/IEC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release subject medical records to employees or agents of the Sponsor, the IRB/IEC, 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 or any other personal information, such as medical record number, any national identification number, etc.

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 UTC, its designee, Lung Biotechnology PBC, and the Investigator.

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

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/IEC 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, the ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify UTC or its designee, Lung Biotechnology PBC, 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 UTC or its designee, Lung Biotechnology PBC, will periodically contact the site and conduct onsite or remote 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 their time and their staff to the monitor to discuss any findings or any relevant issues.

13.4 QUALITY ASSURANCE

The Sponsor is responsible for ensuring that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The Sponsor or a contracted representative of the Sponsor may conduct a quality assurance audit of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant study documents and source data and to allocate time to discuss findings and any relevant issues. In addition, this study is subject to an audit by the relevant Regulatory Authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the inspector direct access to all relevant study documents and source data.

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15 APPENDICES

15.1 PROCEDURE FOR 6-MINUTE WALK TEST

General Procedures:

The 6MWT should be administered consistently at each study site throughout the study. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines and the usual practice of the study site. If the subject was assessed at baseline using oxygen therapy, then all 6MWTs during the study must be conducted with the same oxygen flow rate and mode of administration. Similarly, if the baseline assessment was conducted without oxygen therapy, then subsequent assessments should also be conducted without oxygen therapy. Before each 6MWT, the subject should rest (seated) for at least 10 minutes.

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

Instructions to the Subject:

Subjects will be instructed that the preceding meal should be light. Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes.

The person administering the test will use the following exact dialogue with the subject:

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

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

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

"Do you have any questions about the test?"

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

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

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

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

At 6 minutes, the person administering the test will tell the subject: "Stop where you are."

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

15.2 MODIFIED BORG DYSPNEA SCALE

Immediately following the 6MWT, the person administering the test will obtain a rating of dyspnea using the Borg dyspnea scale. The person will use the following dialogue:

"I would like to use the following scale to indicate the *maximal* shortness of breath you had during the walk test (indicate the Borg dyspnea scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between. For example, if you had shortness of breath somewhere between 4 and 5, you could choose 4.5."

Perceived Breathlessness (Borg Scale)

0 NOTHING AT ALL

0.5 VERY VERY SLIGHT (just noticeable)

1 VERY SLIGHT

2 SLIGHT

3 MODERATE

4 SOMEWHAT SEVERE

5 SEVERE

6

7 VERY SEVERE

8

9 VERY VERY SEVERE (almost maximum)

10 MAXIMUM

15.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (EXAMPLE)

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 ☐

USA / US English version 2

continued

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	☐	☐

USA / US English version 3

continued:..

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

	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 these days.

	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	☐	☐

USA / US English version 4

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.

USA / US English version 6

15.4 UNIVERSITY OF CALIFORNIA SAN DIEGO SHORTNESS OF BREATH QUESTIONNAIRE (EXAMPLE)

UCSD MEDICAL CENTER
PULMONARY REHABILITATION PROGRAM
SHORTNESS-OF-BREATH QUESTIONNAIRE

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Please rate the breathlessness you experience when you do, or if you were to do, each of the following tasks. **Do not skip any items**. If you've never performed a task or no longer perform it, give your best estimate of the breathlessness you would experience while doing that activity. Please review the two sample questions below before turning the page to begin the questionnaire.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1. Brushing teeth ..... **0 1 2 ③ 4 5**

Harry has felt moderately short of breath during the past week while brushing his teeth and so circles a three for this activity.

2. Mowing the lawn ..... **0 1 2 3 4 ⑤**

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past week. She circles a five for this activity.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1.	At rest	**0**	**1**	**2**	**3**	**4**	**5**
2.	Walking on a level at your own pace	**0**	**1**	**2**	**3**	**4**	**5**
3.	Walking on a level with others your age	**0**	**1**	**2**	**3**	**4**	**5**
4.	Walking up a hill	**0**	**1**	**2**	**3**	**4**	**5**
5	Walking up stairs	**0**	**1**	**2**	**3**	**4**	**5**
6.	While eating	**0**	**1**	**2**	**3**	**4**	**5**
7.	Standing up from a chair	**0**	**1**	**2**	**3**	**4**	**5**
8.	Brushing teeth	**0**	**1**	**2**	**3**	**4**	**5**
9.	Shaving and/or brushing hair	**0**	**1**	**2**	**3**	**4**	**5**
10.	Showering/bathing	**0**	**1**	**2**	**3**	**4**	**5**
11.	Dressing	**0**	**1**	**2**	**3**	**4**	**5**
12.	Picking up and straightening	**0**	**1**	**2**	**3**	**4**	**5**

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

13.	Doing dishes	**0**	**1**	**2**	**3**	**4**	**5**
14.	Sweeping /vacuuming	**0**	**1**	**2**	**3**	**4**	**5**
15.	Making bed	**0**	**1**	**2**	**3**	**4**	**5**
16.	Shopping	**0**	**1**	**2**	**3**	**4**	**5**
17.	Doing laundry	**0**	**1**	**2**	**3**	**4**	**5**
18.	Washing car	**0**	**1**	**2**	**3**	**4**	**5**
19.	Mowing lawn	**0**	**1**	**2**	**3**	**4**	**5**
20.	Watering lawn	**0**	**1**	**2**	**3**	**4**	**5**
21.	Sexual activities	**0**	**1**	**2**	**3**	**4**	**5**

How much do these limit you in your daily life?

22.	Shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**
23.	Fear of "hurting myself" by overexerting	**0**	**1**	**2**	**3**	**4**	**5**
24.	Fear of shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**

15.5 PATIENT GLOBAL ASSESSMENT (EXAMPLE)

Question 1: "Over the past week, on average, how many times has **fatigue** limited your ability to do what you wanted?"

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

Question 2: "Over the past week, on average, how many times has **shortness of breath** limited your ability to do what you wanted?"

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

15.6 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

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

"How are you doing (feeling)?"

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

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

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

Using provided definitions, the Investigator will then:

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

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

INTENSITY

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

- Mild: Discomfort noticed, but no disruption to daily activity
- Moderate: Discomfort sufficient to disrupt normal daily activity
- Severe: Inability to work or perform normal daily activity

SERIOUSNESS

An SAE 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[a], is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition).

[a] Hospitalizations that would not be considered SAEs include those for:

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

CAUSALITY

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

Definitions of the causality categories are as follows:

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

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

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION

- Dose Not Changed – The dose or regimen of the study drug was not changed
- Dose Increased – The dose or regimen of study drug was increased
- Dose Decreased – The dose or regimen of study drug was decreased
- Drug Interrupted – Administration of the study drug was stopped temporarily
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted
- Unknown – Changes to the administration of the study drug cannot be determined
- Not Applicable (only used if the AE was started and resolved prior to Tyvaso dosing used in the study treatment periods, or for an AE that started after permanent discontinuation from study treatment)

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.

Signature Page for RIN-PH-304 protocol amend 4 v1.0

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