NCT #: NCT03794583

An Open-Label Extension Study of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)

IND Number 70,362

Protocol RIN-PH-305

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	05 September 2018
Amendment 1 Date:	18 October 2019
Amendment 2 Date:	29 January 2021

LIST OF CONTACTS FOR STUDY

Study Sponsor:	United Therapeutics Corp. [redacted]
Sponsor's Medical Monitor:	[redacted] Telephone: Email: [redacted]
Study Conducted by:	Lung Biotechnology PBC [redacted] [redacted] Telephone: Mobile: Email: [redacted] [redacted] Telephone: Mobile: Email: [redacted] [redacted] Telephone: Mobile: Email: [redacted]
Clinical Laboratory:	Covance Laboratories Inc. [redacted]
Digital Health Technology:	THREAD [redacted] Telephone: Email: [redacted]
SAE Reporting:	United Therapeutics Corp. Global Product Safety & Pharmacovigilance [redacted] Email: Fax: [redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "An Open-Label Extension Study of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)," Amendment 2, dated 29 January 2021 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.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title:	An Open-Label Extension Study of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD)
Phase:	3
Indication:	PH-COPD
Primary Objective:	To evaluate the long-term safety and tolerability of inhaled treprostinil in subjects with PH-COPD.
Secondary Objective:	To evaluate the long-term efficacy of inhaled treprostinil in subjects with PH-COPD.
Exploratory Objective:	[redacted]
Design:	This is a multicenter, open-label extension study for eligible subjects who completed Study RIN-PH-304.
Estimated Duration:	3 years
Sample Size:	Approximately 136 subjects from Study RIN-PH-304 in the **Original Crossover Design** or approximately 314 subjects if the **Contingent Parallel Design** is applied.

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. Completed Study RIN-PH-304.
3. 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 an approved hormonal contraceptive, barrier method [condom or diaphragm] with a spermicide, or an intrauterine device) for the duration of study treatment and for 48 hours after discontinuing study drug.
4. 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.

Exclusion Criteria:	Subjects who meet the following criteria are excluded from the study: 1. Pregnant or lactating. 2. Prematurely discontinued Study RIN-PH-304. 3. Intolerant to inhaled prostanoid therapy. 4. Unwilling or unable to use Sponsor-provided devices (actigraph, spirometer, or smart device). 5. Scheduled to receive another investigational drug, device, or therapy during the course of this study. 6. Any other clinically significant illness or abnormal laboratory value that, in the opinion of the Investigator, might adversely affect the interpretation of the study data or subject safety.
Drug Dosage, Route, and Formulation:	Inhaled treprostinil solution (0.6 mg/mL, 6 mcg/breath), 4 times daily (QID) during waking hours. Subjects will initiate inhaled treprostinil at a dose of 3 breaths QID during waking hours. Study drug doses should be titrated to a target dosing regimen of 15 breaths QID or the maximum tolerated dose. Dose titrations can occur as rapidly as possible (as directed by the Investigator).
Control Group:	None
Procedures:	Subjects cannot begin this open-label extension study until all procedures from Study RIN-PH-304 are complete. The Enrollment Visit for this study will occur on the same day as the final visit for Study RIN-PH-304. At the Enrollment Visit, subjects will receive a new actigraph and continue to use their Sponsor-provided spirometry and smart devices from Study RIN-PH-304 until Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). After the Enrollment Visit, subjects will have assessments at Week 6 and Quarterly thereafter for up to 3 years. Telephone contact will occur weekly during dose titration and then monthly for the remainder of the study to assess tolerability, adverse events, concomitant medications, drug/device compliance, and any other study-related issues, as described in Section 7.4. Given the uncertainty of clinical benefit of novel inhaled treprostinil in PH-COPD and the ongoing COVID-19 pandemic, a high rate of discontinuations and/or missing data are both possible.

	All attempts should be made to have onsite clinic visits, but subjects may have telemedicine visits in lieu of onsite visits, as described in Section 7.5. Safety Assessments: • Adverse events, physical examinations, vital signs, 12-lead electrocardiograms, clinical laboratory assessments, pulmonary function tests, at-home spirometry, and oxygenation will be collected to evaluate the long-term safety and tolerability of inhaled treprostinil. Efficacy Assessments: • N-terminal pro-brain natriuretic peptide, 6-Minute Walk Distance, Borg dyspnea score, patient global assessment, and physical activity (actigraphy) will be collected to evaluate the long-term efficacy of inhaled treprostinil. Exploratory Assessments: • [redacted]
Statistical Considerations:	All safety and efficacy data will be summarized in tables and listings and analyzed for trends over time. No formal hypothesis testing is planned.
Sponsor:	United Therapeutics Corp. [redacted]
Study Conducted by:	Lung Biotechnology PBC [redacted]

TABLE OF CONTENTS

Table of In-Text Tables

LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
AE	Adverse event
BP	Blood pressure
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusion capacity for carbon monoxide
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NT-proBNP	N-terminal pro-brain natriuretic peptide
PE	Physical examination
PFT	Pulmonary function test
PGA	Patient global assessment
PH	Pulmonary hypertension
PH-COPD	Pulmonary hypertension due to chronic obstructive pulmonary disease
QID	4 times daily
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SpO_2	Saturation peripheral capillary oxygenation
TLC	Total lung capacity

1 BACKGROUND AND RATIONALE

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

This open-label extension study will evaluate the safety of continued therapy with inhaled treprostinil in subjects who completed the randomized, placebo-controlled, double-blind, adaptive study, RIN-PH-304. This study hypothesizes that the long-term safety findings will be similar to those observed in Study RIN-PH-304.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the long-term safety and tolerability of inhaled treprostinil in subjects with PH-COPD.

2.2 SECONDARY OBJECTIVE

The secondary objective is to evaluate the long-term efficacy of inhaled treprostinil in subjects with PH-COPD.

2.3 EXPLORATORY OBJECTIVE

[redacted]

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, open-label extension study for subjects who completed Study RIN-PH-304. Subjects who provide informed consent for this study on or prior to the final visit for Study RIN-PH-304 may participate, provided all other eligibility criteria are met. The Enrollment Visit for RIN-PH-305 will occur on the same day as the final visit for Study RIN-PH-304. Study-related procedures and initiation of study drug cannot begin until all final visit procedures for Study RIN-PH-304 are complete.

All subjects will initiate inhaled treprostinil at a dose of 3 breaths (18 mcg) 4 times daily (QID) during waking hours. Dose titrations should occur as rapidly as possible (as directed by the Investigator) with a target dosing regimen of 15 breaths (90 mcg) QID or the maximum tolerated dose. Dosing can be adjusted to tolerability for any dose-related adverse events (AEs). Telephone contact will occur weekly during dose titration and monthly thereafter to assess study drug tolerability, AEs, concomitant medications, drug/device compliance, and any other study-related issues, as described in Section 7.4.

Study visits will occur at Enrollment, Week 6, and Quarterly thereafter for up to 3 years. At the Enrollment Visit, subjects will receive a new actigraph and continue to use their Sponsor-provided spirometry and smart devices from Study RIN-PH-304 for assessment of activity, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), fatigue, and shortness of breath until Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first).

Given the uncertainty of clinical benefit of novel inhaled treprostinil in PH-COPD and the ongoing COVID-19 pandemic, a high rate of discontinuations and/or missing data are both possible. All attempts should be made to have onsite clinic visits, but subjects may have telemedicine visits in lieu of onsite visits, as described in Section 7.5.

The study may be terminated at any time by the Sponsor for reasons that may include, but are not limited to, commercial availability of inhaled treprostinil for PH-COPD and Sponsor termination of the development of the indication for PH-COPD.

A schedule of study visits and assessments is presented in Table 3-1.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Times and Events

Study Procedures	Treatment Phase			
	Enrollment Visit[a]	Week 6 Visit[c] (±3 days)	Quarterly Visits[c] (±14 days)	Discontinuation Visit[m]
Informed Consent	X			
Subject Eligibility	X			
Demographics and Medical History	X[a]			
Physical Examination[r]	X[a]	X	X	X
Vital Signs[e,r]	X[a]	X	X	X
12-Lead ECG[e,r]	X[a]	X	X	X
Clinical Laboratory Assessments[r]	X[a]	X	X	X
NT-proBNP[n,r]	X[a]	X	X	X
Pregnancy Test[d,r]	X[a]	X	X	X
PFTs[i,r]	X[a]	X	X	X
Pulse Oximetry[h,r]	X[a]	X	X	X
6MWT[g,r]	X[a]	X	X	X
Borg Dyspnea Score[f,r]	X[a]	X	X	X
Actigraphy[o]	X	X	X	X
At-home Spirometry[p]	X	X	X	X
PGA[q]	X	X	X	X
Dispense Study Drug/Dosing Instructions	X	X	X	
Drug Administration at Study Site[r]	X	X	X	X
Drug/Device Accountability		X	X	X
Adverse Events[k,l]	X	X	X	X
Concomitant Medications	X	X	X	X
Telephone Contact[j]		X	X	X
Discontinuation Form				X[m]

6MWT, 6-Minute Walk Test; AE, adverse event; BP, blood pressure; eCRF, electronic Case Report Form; DLCO, diffusion capacity for carbon monoxide; ECG, electrocardiogram; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, physical examination; PFT, pulmonary function test; PGA, patient global assessment; PH, pulmonary hypertension; RR, respiratory rate; SpO_2, saturation peripheral capillary oxygenation; TLC, total lung capacity

[a] The following assessments - demographics, medical history, PE, vital signs, 12-lead ECG, clinical laboratory assessments, NT-proBNP, PFTs, pulse oximetry (oxygenation), 6MWT, and Borg dyspnea score - will be performed at the final visit for Study RIN-PH-304 and along with the corresponding eCRF data entry, do not need to be repeated at the Enrollment Visit for RIN-PH-305. Assessments to be performed prior to initiation of study drug include a urine pregnancy test for females of childbearing potential and the collection of biomarkers for consented subjects who did not provide blood in Study RIN-PH-304. If the Enrollment Visit is done via telemedicine, study drug and a new actigraph will be shipped from the study site directly to subjects and subjects should begin study drug and actigraphy assessments as soon as they arrive.

[b] [redacted]

[c] The visit window for the Week 6 Visit is ±3 days; the visit window for all Quarterly Visits is ±14 days. Study visits are scheduled based on the date of enrollment in RIN-PH-305 (eg, 6, 13, 26, 39, 52 weeks after the Enrollment Visit). An unscheduled visit may occur at any time and involve any of the procedures deemed appropriate by the Investigator.

[d] For females of childbearing potential, a urine pregnancy test should be done at the Enrollment Visit (prior to study drug administration) and serum pregnancy tests at all other visits.

[e] Vital signs (weight, RR, HR, and BP) and ECG are to be performed after a 5-minute period of seated rest. No other measurement or procedure should be performed during this 5-minute rest period. When possible, vital signs and ECGs should be collected prior to the 6MWT.

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

[g] See Appendix 15.1. All 6MWTs performed after enrollment will be conducted following at least 10 minutes of seated rest and between 10 to 60 minutes after study drug administration. The 6MWT will be conducted by qualified, trained staff in a designated 6MWT area. Subjects receiving supplemental oxygen during any 6MWT should continue to receive the same flow rate at all subsequent 6MWTs. The supplemental oxygen flow rate (L/min) must be recorded at each study visit, as applicable.

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

[i] PFTs will include the evaluation of FEV_1, FVC, TLC, and DLCO. TLC and DLCO will be assessed only when clinically feasible. When possible, PFTs should be performed prior to the 6MWT. If PFTs cannot be performed prior to the 6MWT, they should be performed after recovery from the 6MWT. If PFTs are done both pre- and post-bronchodilator use, only the post-bronchodilator values will be recorded.

[j] At least weekly telephone contact is required throughout the dose titration period and monthly thereafter for the remainder of the study to assess study drug tolerability, AEs, concomitant medications, drug/device compliance, and any other study-related issues. Subjects will also be directed to call the study site at any time to discuss any issues of concern (AEs, symptoms, concomitant medications, tolerability, etc). Face-to-face interaction may replace telephone contact for the weeks/months where onsite visits occur and the information can be obtained during the visit. All telephone contact must be documented on telephone contact sheets and kept in the subject's source documents.

[k] AEs that are ongoing from Study RIN-PH-304 should be recorded as continuing in RIN-PH-305 and followed as instructed in Section 3.3.2.8.

[l] AEs that are ongoing at study discontinuation in RIN-PH-305 should be followed as instructed in Section 3.3.2.8.

[m] A Discontinuation Visit will be required if the subject cannot be seen at the clinic during a regularly scheduled visit (ie, Week 6 or Quarterly Visit) given the pre-specified visit windows for these study visits. If possible, the subject should remain on study drug until completion of the discontinuation procedures. The study site should complete a Discontinuation Form at the end of the subject's participation in the study, regardless of the visit type.

[n] Blood for NT-proBNP assessment must be drawn prior to the 6MWT and study drug administration.

[o] Subjects will receive a new Sponsor-provided actigraph (activity monitor) at the Enrollment Visit for measurement of daily at-home physical activity. Subjects will be asked to wear the device continuously up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first) with the exception of certain activities of daily living (eg, bathing) or when the actigraph is being charged. Assessment of proper use and data capture should be performed by the study site staff at all scheduled visits.

[p] Subjects will use their Sponsor-provided spirometry device from Study RIN-PH-304 for at-home capture of FEV_1 and FVC data. Subjects will be asked to perform the spirometry assessment at home during the allowable window for each study visit up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). 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 study site staff at all scheduled visits.

[q] Subjects will use their Sponsor-provided smart device from Study RIN-PH-304 for at-home capture of PGA data up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). Subjects will be asked to perform the PGA at the same time as their at-home spirometry assessment. Subjects are encouraged to complete the activity ahead of their scheduled visit. If the PGA is not completed prior to a visit, the subject should complete the PGA during the visit. Assessment of proper use and data capture should be performed by the study site staff at all applicable visits.

[r] Applicable only if an onsite study visit.

3.3 CLINICAL ASSESSMENTS

Safety and efficacy assessments will be performed at all study visits. All attempts should be made to have onsite clinic visits in order to perform these assessments. If the conduct of an onsite visit poses a safety risk due to the COVID-19 pandemic, subjects may have telemedicine visits in lieu of onsite visits, as described in Section 7.5.

3.3.1 Demographics and Medical History

Demographic and medical history information from Study RIN-PH-304 will be used for RIN-PH-305 and should not be re-entered into the electronic Case Report Form (eCRF). Any significant changes in a 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 Safety

The safety of inhaled treprostinil will be evaluated on the following: AEs, physical examinations (PEs), vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory assessments, pulmonary function tests (PFTs), at-home spirometry, and oxygenation. Safety assessments collected as part of the final visit for Study RIN-PH-304 will be used as the Enrollment Visit safety assessments for RIN-PH-305 and do not need to be repeated.

3.3.2.1 Physical Examination

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 the Enrollment Visit should be reported as AEs.

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

3.3.2.2 Vital Signs

Vital signs will be collected at all study visits after at least 5 minutes of seated rest. No other measurement or procedure should be performed during the rest period. When possible, vital signs should be collected prior to the 6-Minute Walk Test (6MWT). Vital signs to be collected include weight, respiratory rate (RR), heart rate (HR), and systolic and diastolic blood pressure (BP). Any clinically significant changes from the Enrollment Visit should be reported as AEs.

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

3.3.2.3 12-Lead Electrocardiogram

A 12-lead ECG will be recorded at all study visits after at least 5 minutes of seated rest. No other measurement or procedure should be performed during the rest period. When possible, the ECG should be collected prior to the 6MWT. Recordings should include Lead II as a rhythm strip, at least 5 QRS complexes, rhythm, HR, PR interval, QT interval, QRS duration, and any abnormalities. Any clinically significant changes from the Enrollment Visit should be reported as AEs.

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

3.3.2.4 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed at all study visits. Laboratory results outside the normal reference range must be assessed for clinical significance by the Investigator. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status. Clinically significant abnormal laboratory results should 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, clinical laboratory assessments will not be performed.

3.3.2.4.1 Chemistry and Hematology Testing

Blood will be collected to assess treatment-emergent changes in the clinical chemistry and hematology tests listed below in Table 3-2.

Table 3-2 Clinical Chemistry and Hematology

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	

3.3.2.4.2 Pregnancy Testing

Females of childbearing potential will undergo a urine pregnancy test at the Enrollment Visit, prior to study drug administration, and a serum pregnancy test at every visit thereafter. A positive pregnancy test will result in a subject's withdrawal from the study.

In the event of Sponsor-approved telemedicine visits, pregnancy tests will not be performed, but subjects will be asked to verbally confirm they are not pregnant. Verbal confirmation of pregnancy will also result in a subject's withdrawal from the study.

Refer to Section 9.4.2 for information related to the reporting and following of pregnancy.

3.3.2.5 Pulmonary Function Tests

Pulmonary function testing should be conducted either before the 6MWT or after recovery from the 6MWT at all study visits. If PFTs are done both pre- and post-bronchodilator administration, only the post-bronchodilator values will be recorded. The following 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 performed.

3.3.2.6 At-home Spirometry

Subjects will use their Sponsor-provided spirometry device from Study RIN-PH-304 for at-home capture of FEV_1 and FVC data.

Subjects will be asked to perform the spirometry assessment at home during the allowable window for each study visit up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). 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 study site staff at all scheduled visits.

3.3.2.7 Oxygenation - Pulse Oximetry

Oxygenation via pulse oximetry will be assessed continuously prior to, during, and immediately following each 6MWT. Pulse oximetry will include the measurement of saturation peripheral capillary oxygenation (SpO_2) and HR. The SpO_2 and HR obtained immediately prior to and immediately following each 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 eCRF.

Study sites must use the same pulse oximeter model from Study RIN-PH-304 to maintain consistency and facilitate documentation of oxygen saturation.

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

3.3.2.8 Adverse Events

Adverse events that are ongoing at the final visit for Study RIN-PH-304 should be recorded in the eCRF as continuing in this study and followed as instructed below.

Subjects should be assessed for AEs from the time they sign the Informed Consent Form (ICF) until study discontinuation or completion. Subjects should be questioned for AEs at all study visits, including telephone contacts and telemedicine visits, and instructed to report all AEs upon occurrence.

All AEs should be followed until resolution (or return to normal/baseline), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE is ongoing at the final study visit.

All serious adverse events (SAEs) should be followed until resolution, death, or the subject is lost to follow-up, even if the SAE is ongoing more than 30 days after the final study visit.

Section 9 and Appendix 15.3 provide guidelines and definitions for the reporting and recording of AEs, respectively.

3.3.2.9 Concomitant Medications

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

3.3.2.9.1 Supplemental Oxygen Use at Rest

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

3.3.3 Efficacy

The efficacy of inhaled treprostinil will be evaluated on the following: N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-Minute Walk Distance, Borg dyspnea score, patient global assessment (PGA), and physical activity (actigraphy). Efficacy assessments collected as part of the final visit for Study RIN PH-304 will be used as the Enrollment Visit efficacy assessments for RIN-PH-305 and do not need to be repeated.

3.3.3.1 N-Terminal Pro-brain Natriuretic Peptide

N-terminal pro-brain natriuretic peptide is a biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). Samples for NT-proBNP will be collected at all study visits and must be drawn prior to the 6MWT and study drug administration.

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

3.3.3.2 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. The 6MWT is to be performed at all study visits. All 6MWTs performed after enrollment must be conducted following at least 10 minutes of seated rest and between 10 to 60 minutes after study drug administration. The 6MWT will be conducted by qualified, trained staff in a designated 6MWT area that meets the requirements described in Appendix 15.1.

Pulse oximetry is to be measured continuously prior to, during, and immediately following each 6MWT, as outlined in Section 3.3.2.7.

If a study 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]), all subsequent 6MWTs should be carried out in a generally consistent manner.

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

3.3.3.2.1 Supplemental Oxygen Use During the 6-Minute Walk Test

Subjects receiving supplemental oxygen during any 6MWT should continue to receive the same flow rate for all subsequent 6MWTs. The amount of supplemental oxygen (L/min) required during any 6MWT should be recorded on the concomitant medication eCRF page. Supplemental oxygen should not be introduced after enrollment, unless there is a medical need in the clinical judgement of the Investigator; however, if supplemental oxygen is started after enrollment, the flow should be consistent for all 6MWTs.

3.3.3.3 Borg Dyspnea Score

The Borg dyspnea score is a 0 to 10 scale rating the level of dyspnea experienced during the 6MWT and should be assessed immediately following each 6MWT. Subjects will be asked to rate their shortness of breath on a scale from 0 (no shortness of breath) to 10 (maximal shortness of breath). The Borg dyspnea scale and instructions for rating the level of dyspnea are provided in Appendix 15.2.

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

3.3.3.4 Patient Global Assessment

The PGA is used to rate subject fatigue and shortness of breath. Subjects will use their Sponsor-provided smart device from Study RIN-PH-304 for at-home capture of PGA data up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). Subjects will be asked to perform the PGA at the same time as their at-home spirometry assessment. Subjects are encouraged to complete the activity ahead of their scheduled visit. If the PGA is not completed prior to a visit, the subject should complete the PGA during the visit. Assessment of proper use and data capture should be performed by the study site staff at all applicable visits. An example of the PGA can be found in Appendix 15.4.

3.3.3.5 Actigraphy

Daily physical activity, including overall, non-sedentary, and moderate to vigorous physical activity will be measured via a wrist-worn medical grade physical activity monitor (actigraph). Subjects will receive a new Sponsor-provided actigraph at the Enrollment Visit for capture of activity data up to Quarterly Visit 4 (Year 1) or the Discontinuation Visit (whichever occurs first). Subjects will be asked to wear the device continuously with the exception of certain activities of daily living (eg, bathing) or when the device is being charged. Assessment of proper use and data capture should be performed by the study site staff at all scheduled visits.

3.3.4 Exploratory

[redacted]

3.3.4.1 [redacted]

[redacted]

[redacted]

3.3.5 Telephone Contact

Telephone contact will occur weekly during the dose titration period and monthly thereafter for the remainder of the study, as described in Section 7.4. Subjects will also be directed to call the study site 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 for the weeks/months where onsite study visits occur and the information can be obtained during the visit. All telephone contact (ie, dosing instructions, reported AEs, and/or medication changes) must be documented on telephone contact sheets and kept in the subject's source documents.

3.4 NUMBER OF SITES

The same study sites that were identified to recruit subjects for Study RIN-PH-304 will be used for RIN-PH-305. Active subjects from Study RIN-PH-304 who meet eligibility criteria will be permitted to enroll in RIN-PH-305.

3.5 NUMBER OF SUBJECTS

The total sample size will be approximately 136 subjects from Study RIN-PH-304 in the **Original Crossover Design** or approximately 314 subjects if the **Contingent Parallel Design** is applied.

3.6 ESTIMATED STUDY DURATION

Subjects will remain in the study from the date their ICF is signed until they withdraw participation, die, are lost to follow-up, or the study ends. It is estimated that the study will last 3 years, but the actual duration may be shorter or longer.

The study is expected to continue until inhaled treprostinil becomes commercially available for PH-COPD or the Sponsor discontinues development for the indication of PH-COPD, whichever occurs first. The Sponsor may discontinue the study for any reason, at any time. The study may also be discontinued if the Investigators and/or Sponsor determine that continuing the study represents a serious medical risk to study subjects.

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. Completed Study RIN-PH-304.
3. 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 an approved hormonal contraceptive, barrier method [condom or diaphragm] with a spermicide, or an intrauterine device) for the duration of study treatment and for 48 hours after discontinuing study drug.
4. 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.

4.2 EXCLUSION CRITERIA

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

1. Pregnant or lactating.
2. Prematurely discontinued Study RIN-PH-304.
3. Intolerant to inhaled prostanoid therapy.
4. Unwilling or unable to use Sponsor-provided devices (actigraph, spirometer, or smart device).
5. Scheduled to receive another investigational drug, device, or therapy during the course of this study.
6. Any other clinically significant illness or abnormal laboratory value that, in the opinion of the Investigator, might adversely affect the interpretation of the study data or subject safety.

4.3 PRESCRIBED THERAPY

There are no restrictions on concomitant medications with the exception of chronic dosing of any other prostanoid therapy. Subjects who require 29 days or more of such therapy must discontinue from this study.

All concomitant medications taken during the conduct of the study, including those taken for AEs or historical medical conditions, should be recorded in the subject's source documents and eCRF. The amount of supplemental oxygen (L/min) required at rest and/or during any 6MWT should be recorded in the subject's source documents and on the concomitant medication eCRF page.

5 SUBJECT ENROLLMENT

Subjects will retain the same subject number they were assigned in Study RIN-PH-304.

5.1 TREATMENT ASSIGNMENT

This is an open-label study and all subjects will receive treatment with the study drug, inhaled treprostinil. This study is not randomized or blinded.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via the Tyvaso Inhalation System, which emits a dose of approximately 6 mcg per breath. Subjects will be provided a Tyvaso Inhalation System by the Sponsor.

All subjects who meet eligibility for RIN-PH-305 will transition from Study RIN-PH-304 and initiate inhaled treprostinil at a dose of 3 breaths (18 mcg) QID during waking hours. Study drug doses should be titrated to a target dosing regimen of 15 breaths (90 mcg) QID or the maximum tolerated dose. Dose titrations can occur as rapidly as possible (as directed by the Investigator). Subjects should be instructed to call the study site if they experience any AEs during the dose titration period.

A sample dose escalation schedule in provided in Table 6-1.

Table 6-1 Sample Inhaled Treprostinil Dose Escalation

Study Day[a]	Single Dose	Total Daily Dose
Titrating to maximum dose of 15 breaths QID		
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 to 30	12 breaths QID (72 mcg)	288 mcg
31 (and beyond)	15 breaths QID (90 mcg)	360 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 only a guide. The Investigator may accelerate or decelerate the dosing titration schedule on an individual basis, considering subject safety, tolerability, and functional improvement.

Dose adjustments should be carried out under appropriate medical supervision and in consultation with the appropriate study site staff. Telephone contact between study site staff and subjects should occur prior to each dose adjustment or at least weekly during dose titration (until 15 breaths QID or the maximum tolerated dose is achieved) and monthly thereafter for the remainder of the study, as described in Section 7.4. All telephone contact (ie, dosing instructions, reported AEs, and/or medication changes) must be documented on telephone contact sheets and kept in the subject's source documents.

If subjects are prescribed bronchodilators, study drug should be administered post-bronchodilator use.

6.2 COMPLIANCE

Study drug (used and unused) must be returned to the study site at each visit and will be dispensed/resupplied, as needed. Study site staff must document the number of used and unused ampoules and assess treatment compliance at each visit.

Subjects will be asked throughout the study whether they have been compliant with study drug dosing instructions. If it is determined that a subject is noncompliant, the study site staff 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.

Subjects will be asked throughout the study whether they have been compliant with actigraphy, spirometry, and smart device use. Assessment of proper use and data capture should be performed by the study site staff at all applicable visits. If it is determined that a subject is noncompliant, the study site staff must re-educate the subject on compliance and its importance.

7 EXPERIMENTAL PROCEDURES

All attempts should be made to have onsite clinic visits. With Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits, as described in Section 7.5.

Refer to Table 3-1 for the schedule of times and events and Table 6-1 for a suggested dose titration schedule.

7.1 ENROLLMENT VISIT

Subjects must sign an approved ICF and meet study-specific inclusion and exclusion criteria before any study-related procedures are performed. The following final visit assessments for Study RIN-PH-304 will serve as the Enrollment Visit assessments for RIN-PH-305: demographics, medical history, PE, vital signs, 12-lead ECG, clinical laboratory assessments, NT-proBNP, PFTs, 6MWT, pulse oximetry (oxygenation), and Borg dyspnea score. As such, these assessments and the corresponding eCRF data entry do not need to be repeated.

The following assessments are required prior to study drug administration:

- Urine pregnancy test (females of childbearing potential)
- [redacted]

The following assessments are required prior to completion of the Enrollment Visit:

- Re-educate subject on the use of inhaled treprostinil with the Tyvaso Inhalation System, and the actigraphy, spirometry, and smart devices, if needed
- Dispense device accessories, as applicable
- Dispense study drug
- Assess for AEs (from the time of informed consent for RIN-PH-305)
- Assess for changes in concomitant medications (from the time of informed consent for RIN-PH-305)

Subjects will be called mid-week following initiation of study drug and routinely thereafter, as described in Section 7.4.

7.2 WEEK 6 VISIT

Subjects are to return to the study site at Week 6 (±3 days). The following sequence of assessments is recommended:

- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- 12-lead ECG (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- PE
- Serum pregnancy test (females of childbearing potential)
- Blood draws for clinical laboratory assessments and NT-proBNP (NT-proBNP must be drawn prior to the 6MWT and study drug administration)
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Study drug administration
- Pulse oximetry (measured continuously prior to, during, and following the 6MWT)
- 6MWT (following at least 10 minutes of seated rest and between 10 to 60 minutes after study drug administration) with documentation of supplemental oxygen requirement, if applicable
- Borg dyspnea score (immediately following the 6MWT)
- Confirm proper use and capture of actigraphy, spirometry, and PGA data
- Assess for AEs
- Assess for changes in concomitant medications
- Dispense study drug/device accessories and assess drug accountability/compliance

In the event of Sponsor-approved telemedicine visits, only the actigraphy, spirometry, PGA, AE, concomitant medication, and drug/device assessments will be performed.

7.3 QUARTERLY VISITS

Subjects are to return to the study site quarterly (±14 days). The following sequence of assessments is recommended:

- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- 12-lead ECG (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- PE
- Serum pregnancy test (females of childbearing potential)
- Blood draws for clinical laboratory assessments and NT-proBNP (NT-proBNP must be drawn prior to the 6MWT and study drug administration)
- [redacted]
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Study drug administration
- Pulse oximetry (measured continuously prior to, during, and following the 6MWT)
- 6MWT (following at least 10 minutes of seated rest and between 10 to 60 minutes after study drug administration) with documentation of supplemental oxygen requirement, if applicable
- Borg dyspnea score (immediately following the 6MWT)
- Confirm proper use and capture of actigraphy, spirometry, and PGA data (up to Quarterly Visit 4 [Year 1] or the Discontinuation Visit [whichever occurs first])
- Assess for AEs
- Assess for changes in concomitant medications
- Dispense study drug/device accessories and assess drug accountability/compliance

In the event of Sponsor-approved telemedicine visits, only the actigraphy, spirometry, PGA, AE, concomitant medication, and drug/device assessments will be performed.

7.4 TELEPHONE CONTACTS

Subjects will be called mid-week following initiation of study drug to perform dose titration and discuss study drug tolerability and any study-related issues.

At least weekly telephone contact is required throughout the dose titration period (until 15 breaths QID or the maximum tolerated dose is achieved) to assess study drug tolerability, AEs, concomitant medications, drug/device compliance, and any other study-related issues. Face-to-face interaction may replace telephone contact for the weeks where onsite study visits occur and the information can be obtained during the visit.

At least monthly telephone contact is required after the dose titration period is complete (15 breaths QID or the maximum tolerated dose is achieved) for the remainder of the study to assess study drug tolerability, AEs, concomitant medications, drug/device compliance, and any other study-related issues. Face-to-face interaction may replace telephone contact for the months where onsite study visits occur and the information can be obtained during the visit.

Subjects will also be directed to call the study site or Investigator at any time to discuss any issues of concern (AEs, symptoms, tolerability, device issues, etc). All telephone contact (ie, dosing instructions, reported AEs, and/or medication changes) must be documented on telephone contact sheets and kept in the subject's source documents.

7.5 TELEMEDICINE VISITS

All attempts should be made to have onsite clinic visits. With Sponsor approval, subjects may have telemedicine visits in lieu of onsite visits, if the conduct of an onsite clinic visit poses a safety risk due to the COVID-19 pandemic. The following assessments will be performed during telemedicine visits:

- Confirm proper use and capture of actigraphy, spirometry, and PGA data (up to Quarterly Visit 4 [Year 1] or the Discontinuation Visit [whichever occurs first])
- Assess for AEs
- Assess for changes in concomitant medications
- Assess study drug accountability/compliance
- Confirm receipt of study drug/device accessories
- Confirm the subject is not pregnant (females of childbearing potential)

If the Enrollment Visit is done via telemedicine, study drug and a new actigraph will be shipped from the study site directly to subjects and subjects should begin study drug and actigraphy assessments as soon as they arrive.

7.6 UNSCHEDULED VISIT

An Unscheduled Visit may occur at any time and may involve any study-related procedures deemed appropriate by the Investigator.

7.7 DISCONTINUATION VISIT

This visit is required if the subject cannot be seen during a regularly scheduled study visit (ie, Week 6 or Quarterly Visit) to undergo discontinuation procedures. If possible, the subject should remain on study drug until completion of the discontinuation procedures. The following sequence of assessments is recommended:

- Vital signs: weight, RR, HR, and BP (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- 12-lead ECG (following at least 5 minutes of seated rest; no other measurement or procedure should be performed during the rest period)
- PE
- Serum pregnancy test (females of childbearing potential)
- Blood draws for clinical laboratory assessments and NT-proBNP (NT-proBNP must be drawn prior to the 6MWT and the last study drug administration, if possible)
- [redacted]
- PFTs (performed before the 6MWT or after recovery from the 6MWT)
- Study drug administration
- Pulse oximetry (measured continuously prior to, during, and following the 6MWT)
- 6MWT (following at least 10 minutes of seated rest and between 10 to 60 minutes after the last study drug administration, if possible) with documentation of supplemental oxygen requirement, if applicable
- Borg dyspnea score (immediately following the 6MWT)
- Confirm capture of actigraphy, spirometry, and PGA data
- Assess for AEs
- Assess for changes in concomitant medications
- Collect study drug and perform final drug accountability

- Collect the Tyvaso Inhalation System, actigraph, spirometry, and smart devices
- Complete the Discontinuation Form

The study site should complete a Discontinuation Form at the end of the subject's participation in the study, regardless of the visit type.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

Subjects may voluntarily withdraw from the study at any time, for any reason after completing a formal and written withdrawal of consent. Subject withdrawal of consent would preclude data collection after the date the withdrawal of consent was documented.

The Investigator should make every effort to perform all scheduled evaluations prior to study discontinuation.

A positive pregnancy test or verbal confirmation of pregnancy will result in a subject's withdrawal from the study. Refer to Section 9.4.2 for information related to the reporting and following of pregnancy.

In the event a subject discontinues study drug prematurely due to an AE, the subject will be followed, as instructed in Section 9.3. The study site should complete a Discontinuation Form at the end of the subject's participation in the study, regardless of the visit type.

8.2 CRITERIA FOR STUDY TERMINATION

The study may be stopped at any time if, in the opinion of the Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs, or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.3 CRITERIA FOR SITE DISCONTINUATION

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

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

9 ADVERSE EVENT REPORTING

All AEs that occur while a subject is participating in this study will be documented, as outlined in 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, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable or 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, in the view of the Investigator, 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 study completion or early termination. Any 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. Refer to Appendix 15.3 for guidelines and definitions for recording AEs. 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

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. Applicable eCRF pages should be updated with new or additional information, as appropriate.

All AEs should be followed until resolution (or return to normal/baseline), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE is ongoing at the final study visit.

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

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

9.4.1 Serious Adverse Event Reporting

Study sites should enter all available initial and follow-up SAE information in the eCRF (primary method) within 24 hours of awareness, regardless of causality or expectedness. The SAE information will be directly transmitted from the eCRF into the safety database (Argus) for review by Drug Safety. If the study site is unable to enter the SAE information into the eCRF within 24 hours of awareness, the alternative 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 in 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]. All subject identifiers (eg, name, medical record number, birth date) must be redacted by the study site before sending to the Sponsor. 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, as per local requirements. Copies of each notification and subsequent documentation of the IEC/IRB/local equivalent body 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 within 24 hours of awareness via email [redacted] or fax [redacted] using the Pregnancy Notification and Outcome Form. All pregnancies, including those of a male subject's female partner, must be followed until outcome. Pregnancy is not an AE. 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.

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 clinical database lock.

Any changes in the statistical methods described in this protocol that occur prior to clinical database lock will be documented in the SAP and will not require a protocol amendment.

10.1 DATA PROCESSING

The eCRF is the primary data collection instrument for the study. All data requested in the eCRF must be recorded following the eCRF completion guidelines provided to the study site. Data will be entered in the eCRF for all subjects who sign an ICF up until study completion or discontinuation. Data recorded in the eCRF should be consistent with source documents. A representative from the Sponsor will verify eCRF data fields against source documents per the established monitoring plan. Data transmitted from the study 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 eCRF to signify their approval of the data. The Investigator will be required to re-sign an eCRF if changes are made by the study site after the Investigator initially signs the eCRF. The clinical database will be final when all outstanding queries are 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

No formal sample size calculation has been conducted. Eligible subjects from Study RIN-PH-304 may enter this study.

10.3 ANALYSIS PLAN

All safety and efficacy data will be summarized in tables and listings and analyzed for trends over time. No formal hypothesis testing is planned. The SAP will detail the specific analyses and methods.

10.3.1 Safety Analyses

The Safety Population will be defined as all subjects in the study that receive inhaled treprostinil at any time during the course of the study. Safety analyses will be performed on the Safety Population. Treatment-emergent AEs and changes in PEs, vital signs, ECGs, clinical laboratory assessments, PFTs, at-home spirometry, and oxygenation will be the primary assessments of safety. All reported AEs will be assigned Preferred Terms per the Medical Dictionary for Regulatory Activities.

10.3.2 Efficacy Analyses

The effect of inhaled treprostinil will be evaluated on changes from baseline in NT-proBNP, 6-Minute Walk Distance, Borg dyspnea score, PGA, and physical activity (actigraphy).

10.3.3 Exploratory Analyses

[redacted]

10.4 INTERIM ANALYSIS

Interim analyses for safety data will be performed as needed by the Sponsor for regulatory submissions and other purposes. Given the open-label nature of the study, the Sponsor may tabulate study data and present or publish such data during the course of the study.

10.5 OTHER ANALYSES

Other analyses may be conducted based on available study data. Details of 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.

11 PACKAGING AND FORMULATION

11.1 STUDY SUPPLIES

11.1.1 Actigraphy, Spirometry, and Smart Devices

Subjects will receive a new actigraph at enrollment and continue to use their Sponsor-provided spirometry and smart devices from Study RIN-PH-304.

If a device is defective or suspected to be defective and the issue cannot be resolved via troubleshooting, the study site should complete a THREAD Help Desk Ticket. A replacement device will be issued to the subject. Replacement devices will be provided using standard packaging labeled with the study number and accompanied by the Instructions for Use.

11.2 CONTENTS

11.2.1 Study Drug

The Sponsor will supply study drug (treprostinil inhalation solution, 0.6 mg/mL) as clear liquid packaged 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 and sealed in aluminum foil pouches that are placed inside a carton (containing 12 pouches per carton). Subjects will be supplied enough cartons to cover the QID dosing between study visits.

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

11.2.2 Study Inhalation Device

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via the Tyvaso Inhalation System. Subjects will be provided a Tyvaso Inhalation System by the Sponsor.

If a device is defective or suspected to be defective and the issue cannot be resolved via troubleshooting, the study site should complete a Product Complaint Form (provided in the Study Procedures Manual), submit it to the Sponsor within 24 hours of awareness, and follow any additional instructions provided by the Sponsor. Damaged devices will be replaced as needed during the study.

11.3 LABELING

11.3.1 Study Drug

The aluminum foil pouches (containing the ampoules) and the outer carton will be labeled with the same information. At a minimum, the outer packaging (pouch and carton) will be labeled to clearly disclose the product name, study number, kit identification number, expiration 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 device accessories will be supplied using standard packaging and labeled with the study number.

11.4 STORAGE AND HANDLING OF STUDY DRUG

All study drug must be stored at room temperature 77°F (~25°C) with excursions permitted to 59°F to 86°F (15°C to 30°C). 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 a foil pouch is opened, the study drug ampoules inside should be used within 7 days. Refer to the study drug label for information on use and storage of the product.

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

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.

To accommodate Sponsor-approved telemedicine visits, study drug and device accessories may be shipped directly to the subject.

Subjects should return all Sponsor-provided devices and any remaining study drug to the study site at the end of their study participation (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 and device accountability and reconciliation overall and on a per subject basis. Accountability records are to be maintained throughout the study and these records include, but are not limited to, the amount of study drug and devices received from the Sponsor, the amount dispensed to each subject, and the amount returned to the study site from the subject.

At each study visit, study site staff will:

- Collect and document all used/unused study drug and any devices/device accessories dispensed and returned.
- Assess study drug compliance per the dosing instructions given at the previous study visit.
- Re-educate the subject about the importance of compliance with the prescribed dosing regimen and device-related assessments (if compliance is low).

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

Once the Sponsor confirms drug accountability for a completed subject, the study site may destroy the used/unused study drug locally (with a destruction certification placed in the subject's file) or ship it to a Sponsor-designated location for destruction. Refer to the Study Procedures Manual regarding the return of Sponsor-provided devices for a completed subject.

12 REGULATORY AND ETHICAL OBLIGATIONS

12.1 US FDA OR APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with ICH and GCP guidelines and all applicable national regulations. The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to regulatory authorities and any IRB/IEC that requires it. Any additional national reporting requirements as 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 designee(s) 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's 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 study site, the Investigator will obtain approval for the study from an appropriate IRB/IEC and provide the Sponsor 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/IEC following study completion or termination according to the IRB/IEC standard procedures. Additional updates will be provided in accordance with the IRB/IEC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

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

Study sites will be required to provide the following documents to United Therapeutics Corporation's designee (Lung Biotechnology PBC): signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/IEC composition and roster, IRB/IEC protocol and ICF approval letters, and Curriculum Vitae of the study staff listed on Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep subject medical information confidential. United Therapeutics Corporation, Lung Biotechnology PBC, the FDA, 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, the FDA, or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects, but no published information will identify any subject's name or any other personal information, such as medical record number, 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 United Therapeutics Corporation's 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 United Therapeutics Corporation 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, the ICH, and GCP guidelines, Monitors for United Therapeutics Corporation or its designee, Lung Biotechnology PBC, will periodically contact the study site and conduct onsite or remote monitoring 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, periodically verify drug accountability, 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 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.

14 REFERENCES

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

Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest. 2006;129(5):1313-1321.

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

Klinger JR. Group III Pulmonary Hypertension: pulmonary hypertension associated with lung disease: epidemiology, pathophysiology and treatments. Cardiol Clin. 2016;34(3):413-433.

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. Subjects receiving supplemental oxygen during their baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. 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 stopwatch. 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 out, “stop where you are” while simultaneously stopping the watch, and then measuring 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 <u>exact</u> 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 at the end (eg, chair), 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 again. 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 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 Dyspnea 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 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
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 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

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, may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication and not associated with any deterioration in condition (eg, hospitalization for a routine right heart catheterization).
- Treatment that was elective or pre-planned for a pre-existing condition and not associated with any deterioration in condition (eg, pre-planned operation that does not lead to further complications).
- 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 - 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 on 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 study drug was stopped temporarily
- Drug Withdrawn: Administration of study drug was stopped permanently
- Unknown: Changes to the administration of the study drug cannot be determined
- Not Applicable: Only used if the AE started and resolved prior to study drug dosing, or for an AE that started after permanent discontinuation of 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

15.4 PATIENT GLOBAL ASSESSMENT (EXAMPLE)

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

- Always
- Often
- Sometimes
- Rarely
- Never

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

- Always
- Often
- Sometimes
- Rarely
- Never

Signature Page for RIN-PH-305 Protocol Amendment 2 v1.0

Approver Task	[redacted] 28-Jan-2021 16:28:49 GMT+0000

Approver Task	[redacted] 28-Jan-2021 17:05:43 GMT+0000

Approver Task	[redacted] 29-Jan-2021 19:28:02 GMT+0000

Approver Task	[redacted] 29-Jan-2021 20:10:10 GMT+0000

Approver Task	[redacted] 30-Jan-2021 02:53:19 GMT+0000