A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Inhaled Treprostinil in Subjects with Idiopathic Pulmonary Fibrosis

IND# 149,587

RIN-PF-301

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol amendment 4 entitled "A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Inhaled Treprostinil in Subjects with Idiopathic Pulmonary Fibrosis" dated 26 July 2023 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference for Harmonisation (ICH) Guideline for Good Clinical Practice and any applicable 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. (UTC).

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

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

Note that throughout this clinical study protocol, use of the word *should* means that something is suggested or recommended, but not required.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

PROTOCOL SYNOPSIS

Title	A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Inhaled Treprostinil in Subjects with Idiopathic Pulmonary Fibrosis
Study Phase	3
Indication	Idiopathic pulmonary fibrosis (IPF)
Primary Objective	The primary objective of RIN-PF-301 is to evaluate the superiority of inhaled treprostinil against placebo for the change in absolute forced vital capacity (FVC) from baseline to Week 52.
Primary Endpoint	The primary efficacy endpoint of the study is the change in absolute FVC in subjects with IPF from baseline to Week 52.
Secondary Endpoints	Secondary efficacy endpoints of the study are: • Time to clinical worsening (including time to death, respiratory hospitalization, or ≥10% relative decline in % predicted FVC) • Time to first acute exacerbation of IPF • Overall survival at Week 52 • Change from baseline in % predicted FVC at Week 52 • Change from baseline in King's Brief Interstitial Lung Disease Questionnaire score at Week 52 • Change from baseline in diffusion capacity of lungs for carbon monoxide at Week 52
Exploratory Endpoints	Exploratory efficacy endpoints of the study are: • Change from baseline in absolute FVC at Weeks 16, 28, and 40 • Change from baseline in N-terminal pro-brain natriuretic peptide at Week 52 • Change from baseline in resting supplemental oxygen use at Week 52 • Evaluation of pharmacogenomics and biomarkers for subjects who consent to collection
Safety Endpoints	Safety will be assessed by reviewing the following parameters: • Adverse events (AEs) and serious AEs • Clinical laboratory parameters • Vital signs, including saturation of peripheral capillary oxygenation • 12-lead electrocardiograms
Study Design	This is a Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of subjects with IPF treated with inhaled treprostinil over a 52-week period.
Sample Size	The total sample size is planned to be approximately 576 subjects.

Summary of Subject Eligibility Criteria	Eligible subjects must be ≥40 years of age at the time of signing informed consent; have a diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu 2018) and confirmed by central review of high-resolution computed tomography imaging and if available, surgical lung biopsy; and have a FVC ≥45% predicted. Subjects on pirfenidone or nintedanib must be on a stable and optimized dose for ≥30 days prior to Baseline. Subjects with forced expiratory volume in 1 second (FEV_1)/FVC <0.70, those on >10 L/min of supplemental oxygen at rest at Baseline, and women who are pregnant or lactating will not be eligible to participate in the study.
Drug Dosage and Formulation	Study medication (treprostinil inhalation solution, 0.6 mg/mL or placebo) will be supplied as clear liquid in 2.9-mL ampules. Subjects will be randomly assigned 1:1 to inhaled treprostinil or placebo at Baseline. Randomization will be stratified by IPF background therapy (nintedanib or pirfenidone vs. no background therapy). All subjects will initiate inhaled treprostinil (6 mcg/breath) or placebo at a dose of 3 breaths (18 mcg) administered 4 times daily (QID; during waking hours) and will titrate to a target dosing regimen of 12 breaths (72 mcg) QID. Study drug doses may be titrated up every 3 days, as tolerated, by administering an additional 1 breath (6 mcg) per treatment session, QID, until the target dose of 12 breaths QID is reached or the subject reaches their maximum clinically tolerated dose. As needed, Investigators may extend the time between dose increases. Each subject's dose should be maximized throughout the study.
Control Group	Placebo
Route of Administration	Inhaled: Treprostinil inhalation solution or placebo will be administered using the TD-300 ultrasonic nebulizer (Tyvaso Inhalation System®).
Procedures	Subjects will be assessed during the Screening and Baseline Visits to determine eligibility for the study. Once eligible, 6 Treatment Period visits to the clinic will be required at Weeks 4, 8, 16, 28, 40, and 52. Subjects will also be contacted by telephone or email at least weekly until Week 16 and monthly thereafter in-between study visits to discuss study drug titration, assess study drug tolerability, monitor AEs, and document changes to concomitant medications. Subjects who discontinue study drug prematurely before Week 52 will be encouraged to remain in the study and attend the remaining scheduled study visits up to and including Week 52; a Premature Study Drug Discontinuation Visit should be conducted as soon as possible, and as best as possible prior to final dose of study drug. In the event a subject withdraws from the study, an Early Termination (ET) Visit will be conducted; all assessments planned for the Week 52 Visit will be conducted during the ET Visit, as applicable. ET Visit assessments should be completed before the final dose of study drug if at all possible. Every attempt will be made to assess vital status for all subjects at Week 52, including those who discontinue the study prematurely or who withdraw consent.

	Subjects who complete the Week 52 Visit may be offered the opportunity to enter an open-label extension study after completing the final study visit. Key Assessments: • Spirometry (FEV_1, FVC) • King's Brief Interstitial Lung Disease Questionnaire • N-terminal pro-brain natriuretic peptide • Diffusion capacity of lungs for carbon monoxide • Resting supplemental oxygen use • Urine pregnancy tests for women of childbearing potential • Clinical laboratory tests • Vital signs, including resting saturation of peripheral capillary oxygenation • 12-lead electrocardiogram • Assessment of hospitalizations • Assessment of acute exacerbations of IPF • AE and serious AE assessments • Whole genome sequencing for subjects who consent to the pharmacogenomic sample collection • Analysis of biomarkers (specific targets to be determined) for subjects who consent to the biomarker sample collection • Vital status
Statistical Considerations	A sample size of 472 subjects will have at least 80% power to detect a difference in means of 80 mL in change from baseline to Week 52 in absolute FVC, assuming that the common standard deviation is 300 mL using a 2-group t-test with a 0.05 two-sided significance level. Assuming an 18% dropout rate, approximately 576 subjects need to be randomized. The primary efficacy endpoint of change in absolute FVC from baseline to Week 52 will be analyzed using mixed model repeated measures or a corresponding non-parametric method when assumptions for mixed model repeated measures are violated. A Data Monitoring Committee will be established and will meet on a regular basis to monitor safety throughout study conduct.
Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709 USA

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWD	6-Minute Walk Distance
AE	Adverse event
AZA	Azathioprine
CEC	Clinical Endpoint Committee
CI	Confidence interval
DLCO	Diffusion capacity of lungs for carbon monoxide
DMC	Data Monitoring Committee
DP1	Prostaglandin D receptor 1
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EP2	Prostaglandin E receptor 2
ET	Early Termination
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HRCT	High-resolution computed tomography
ICF	Informed consent form
ICH	International Council of Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
ILD	Interstitial lung disease
IP	Prostacyclin receptor
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent-to-treat
IXRS	Interactive voice/web response system
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
MMRM	Mixed model repeated measures
NT-proBNP	N-terminal pro-brain natriuretic peptide
OCS	Oral corticosteroids
OLE	Open-label extension
PAH	Pulmonary arterial hypertension
PDE5-I	Phosphodiesterase type 5 inhibitors
PGE2	Prostaglandin E2
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease
QID	4 times daily
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SpO_2	Saturation of peripheral capillary oxygenation
TGF-β	Transforming growth factor beta
UIP	Usual interstitial pneumonia
UTC	United Therapeutics Corp.

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Interstitial lung disease (ILD) encompasses a heterogeneous group of parenchymal lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs within the lungs (Travis 2013, Seeger 2013). Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs. The symptomatology of ILD is nonspecific and covers a wide range of symptoms, and severity of symptoms can vary substantially among patients. Only 2 therapies are currently approved by the Food and Drug Administration (FDA) for ILD indications in the US, nintedanib (Ofev®) and pirfenidone (Esbriet®). Nintedanib is a kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis (IPF), chronic fibrosing ILDs with a progressive phenotype, and systemic sclerosis-associated ILD (Ofev Prescribing Information 2020). Pirfenidone belongs to the pyridone class and is approved for the treatment of IPF (Esbriet Prescribing Information 2019).

IPF, a distinct type of ILD, is a serious, chronic, progressive, fibrosing interstitial pneumonia with no known cause typically occurring in patients above 50 years of age (Raghu 2018). It is characterized by progressive fibrosis, lung scarring, and a radiological pattern known as usual interstitial pneumonia (UIP) (Cottin 2018). IPF is defined by the presence of a radiographic and/or a histopathological pattern of UIP in the absence of an alternate etiology for this pattern. UIP usually presents as “honeycombing” (subpleural cystic airspaces with well-defined walls), traction bronchiectasis (dilatation of the bronchi), and peripheral alveolar septal thickening. IPF is associated with increasing cough and dyspnea, greatly impacts patient quality of life, and eventually leads to death from respiratory failure or complicating comorbidities. Diagnosis is based on the exclusion of other ILDs and similar conditions, and the identification of the UIP pattern on high-resolution computed tomography (HRCT) scan and/or surgical lung biopsy (Martinez 2017).

Currently there is no cure for IPF, and only 2 drugs are approved to treat the condition (nintedanib and pirfenidone). While results from a randomized study show that nintedanib slows the rate of decline in forced vital capacity (FVC), additional treatment options for IPF are needed, as pulmonary fibrosis continues to confer high morbidity and mortality despite currently

available treatments (Montesi 2020). The results of RIN-PH-201 (INCREASE) (Section 1.2.3) in patients with pulmonary hypertension (PH) associated with ILD (PH-ILD) provide evidence that inhaled treprostinil may offer a treatment option for patients with IPF.

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 benzindene analogue of prostacyclin. Prostacyclin is known to lower pulmonary artery pressure, increase cardiac output without affecting the heart rate, improve systemic oxygen transport, and possibly reverse pulmonary arterial remodeling. The pharmacology of treprostinil is well-characterized, and treprostinil is approved for the treatment of pulmonary arterial hypertension (PAH) following the subcutaneous, intravenous, inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

Treprostinil is a full agonist at the prostacyclin receptor (IP) and potently activates the prostaglandin E receptor 2 (EP2) and the prostaglandin D receptor 1 (DP1). In diseased lung, there is a profound decrease in IP and an upregulation of EP2, which affects the action of prostacyclin mimetics. Therefore, the role of EP2 as a negative modulator of vascular tone, proliferation, and fibrosis is important to consider and suggests that treprostinil could provide additional benefits as an anti-fibrotic agent, even in the absence of or reduced expression of the IP receptor (Clapp 2020).

EP2 activation has been reported to inhibit mast cell-mediated bronchoconstriction (Safholm 2015). Furthermore, mast cells are thought to promote vascular remodeling in lung disease by releasing histamine, prostaglandin D2, leukotrienes, pro-inflammatory cytokines, and growth factors, such as transforming growth factor beta (TGF-β) (Arthur 2016). Activation of EP2 receptors has a range of inhibitory effects on fibroblast function that may be beneficial in patients with IPF. Cultured lung fibroblasts from IPF patients have a diminished capacity to synthesize prostaglandin E2 (PGE2) and to express cyclooxygenase-2 (Wilborn 1995); supplementation with treprostinil to activate EP2 may therefore be beneficial. For example, treatment of human lung fibroblasts with either PGE2 or butaprost, a selective EP2 agonist,

inhibits migration (White 2005). In addition, PGE2 inhibits the transition of fibroblasts to myofibroblasts (Kolodsick 2003) and suppresses fibroblast proliferation and collagen synthesis through EP2 receptor-mediated pathways (Moore 2005).

Anti-fibrotic properties for treprostinil have also been reported both in vivo using the bleomycin-induced pulmonary fibrosis model and in vitro via inhibition of TGF-β-stimulated collagen production in primary human lung fibroblasts (Corboz 2018, Nikitopoulou 2019, Lambers 2018). Similarly, activation of DP1 receptor, another prostaglandin receptor for which treprostinil has very high potency, significantly decreased both inflammatory cell recruitment and collagen accumulation in the lung (van den Brule 2010). In addition, treprostinil has been shown to inhibit the recruitment of bone marrow-derived circulating fibrocytes to sites of vascular remodeling (Nikam 2010). Furthermore, human fibrocytes express IP and EP2 receptors, and cell–matrix adhesion was significantly impaired by treatment with treprostinil, a mechanism shown to involve limiting the activity of extracellular signal-regulated kinase via the cyclic adenosine monophosphate–Rap axis to inhibit the adhesion and differentiation of fibrocytes (Nikam 2011).

Additional support for treprostinil as an effective treatment option for pulmonary fibrosis comes from a high-throughput screen to assess the therapeutic potential of novel drugs in pulmonary fibrosis, which identified drugs acting at EP2 as among the most effective agents at inhibiting TGF-β-induced myofibroblast differentiation (Sieber 2018).

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 chronic administration to patients (Remodulin® [treprostinil] injection Prescribing Information 2021).

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 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

Inhaled treprostinil was approved in the US in 2009 (New Drug Application 022387), Israel in 2010, Argentina in 2015, Japan in 2022, and Colombia in 2023 for the treatment of PAH (World Health Organization Group 1) to improve exercise ability demonstrated by an increase in 6-Minute Walk Distance (6MWD). Additionally, inhaled treprostinil was approved in the US (2021), Israel (2022), and Argentina (2023) for the treatment of PH-ILD (World Health Organization Group 3). As of 21 May 2023, approximately 1291 subjects have received treprostinil by inhalation across various studies, ranging from acute studies in healthy volunteers to long-term treatment in subjects with various types of PH and fibrotic lung disease. Clinical studies of inhaled treprostinil include an absolute systemic bioavailability study, a thorough QTc study in healthy volunteers (preceded by a dose range-finding study), the pivotal safety and efficacy study (LRX-TRIUMPH 001, also called TRIUMPH-I) conducted in subjects with PAH, the long-term Phase 4 safety and quality of life study (RIN-PH-401) in subjects with PAH transitioning from inhaled iloprost to inhaled treprostinil, and the pivotal safety and efficacy study (RIN-PH-201) conducted in subjects with PH-ILD and its open-label extension (OLE) study (RIN-PH-202). Additionally, a long-term, respiratory tract, safety registry study (RIN-PH-403) and a dosing and titration registry study (RIN-PH-404) have been completed. United Therapeutics Corp. (UTC) is conducting a replicate, Phase 3 study of RIN-PF-301 globally (RIN-PF-303), which is currently ongoing, and an OLE study (RIN-PF-302).

The INCREASE study (RIN-PH-201) was a multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group study, designed to investigate the safety and efficacy of inhaled treprostinil in 326 subjects with PH-ILD. Subjects in the study received treatment with inhaled treprostinil or placebo and titrated up to a maximum dose of 12 breaths (72 mcg) 4 times daily (QID). The primary efficacy endpoint was change in peak 6MWD at Week 16. Additional assessments included change in N-terminal pro-brain natriuretic peptide

(NT-proBNP) at Week 16, time to clinical worsening, time to exacerbation of underlying disease, and evaluations of pulmonary function tests.

Subjects receiving inhaled treprostinil experienced a significant improvement in peak 6MWD compared to placebo beginning at Week 8 and continuing to Week 16. Using nonparametric analysis of covariance and Hodges-Lehmann estimates, treatment increases in peak 6MWD were observed at Week 8 (15.0 m; p=0.0104), Week 12 (20.0 m; p=0.0041), and Week 16 (21.0 m; p=0.0043). Using the mixed model repeated measures (MMRM) method, treatment increases in peak 6MWD were more pronounced at Week 8 (24.1 m; p=0.0002), Week 12 (31.3 m; p<0.0001), and Week 16 (31.1 m; p<0.0001). All the secondary endpoints of this study were also significantly improved for subjects receiving inhaled treprostinil; plasma NT-proBNP was lower at Week 8 (26% reduction; p=0.0007; 95% confidence interval [CI]: 0.62, 0.88) and Week 16 (42% reduction; p<0.0001; 95% CI: 0.47, 0.72), the risk of experiencing a clinical worsening event was reduced by 39% (hazard ratio [95% CI] of 0.61 [0.40, 0.92]; p=0.0202), and change from baseline in trough 6MWD at Week 15 was higher (15.0 m; p=0.0432).

Pulmonary function testing was initially conducted in RIN-PH-201 as a safety assessment (Safety Population) during the study. The results indicated that although most parameters remained stable for subjects in the study, a notable improvement in FVC (% predicted) was observed at Week 16 in the inhaled treprostinil group (Nathan 2021). As a result, post hoc MMRM analyses of FVC data were performed for the Intent-to-treat (ITT) Population. These analyses revealed that treatment with inhaled treprostinil resulted in significant improvements in % predicted FVC at Weeks 8 and 16, with subjects having underlying etiologies of idiopathic interstitial pneumonias (Week 8: 2.0%, p=0.037 and Week 16: 2.9%; p=0.0096) and IPF (Week 8: 2.5%; p=0.038 and Week 16: 3.5%; p=0.015) showing greater improvement. Consistent positive effects were also seen in patients with chronic hypersensitivity pneumonitis and environmental/occupational lung disease (Nathan 2021).

Additionally, exacerbations of underlying lung disease (defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality) were evaluated as a safety endpoint in the study. Overall, 43 (26.4%) subjects in the inhaled treprostinil group compared with 63 (38.7%) subjects in the placebo group

experienced an exacerbation of underlying lung disease during the study (p=0.018). The comparison of the Kaplan-Meier estimates of the time to first exacerbation of underlying lung disease between the inhaled treprostinil group and the placebo group was significant (log rank test: p=0.0396). The Cox proportional hazard model gave a hazard ratio (95% CI) of 0.66 (0.45, 0.97) (p=0.0338), demonstrating that treatment with inhaled treprostinil provided a 34% overall reduction in the risk of an exacerbation of underlying lung disease during the study.

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE

The INCREASE study demonstrated that inhaled treprostinil resulted in significant improvements in % predicted FVC in subjects with PH due to IPF, but it also reduced acute exacerbations of underlying lung disease in the overall PH-ILD population (Section 1.2.3). Additionally, anti-fibrotic properties for treprostinil have been reported both in vivo using the bleomycin-induced pulmonary fibrosis model and in vitro via inhibition of TGF-β-stimulated collagen production in primary human lung fibroblasts (Corboz 2018, Nikitopoulou 2019, Lambers 2018). Treprostinil has also been shown to restore maximal bronchodilation in bronchial smooth muscle isolated from patients with World Health Organization Group 3 PH (Ozen 2020) and to affect extracellular matrix remodeling and fibrosis by reducing recruitment of fibrocytes to sites of vascular remodeling (Nikam 2010).

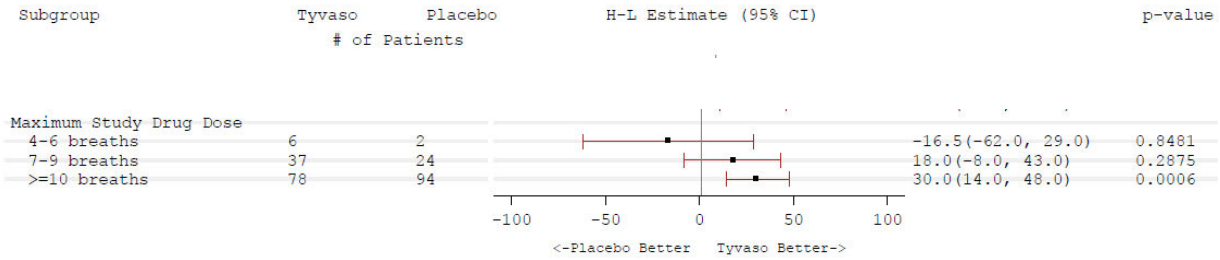
The improvements in FVC and reduced exacerbations of underlying lung disease from the INCREASE study, combined with the preclinical evidence of antifibrotic activity of treprostinil, suggest that inhaled treprostinil may offer a treatment option for patients with IPF.

1.3.1 Rationale for Dosing Regimen in RIN-PF-301

Overall systemic exposure with inhaled treprostinil is low relative to other treprostinil formulations (Kumar 2016), and dosing is driven primarily by tolerability. The 2 initial dose selection studies of inhaled treprostinil in patients with PAH (Voswinckel 2006, Channick 2006) helped to define the inhalation formulation, the dose-response relationship, tolerability, and safety, and provided the basis for conducting the pivotal Phase 3 study, TRIUMPH I. The INCREASE study further validated tolerability of the selected titration schedule (frequency) and the dosing regimen of up to 12 breaths (72 mcg) in patients with PH due to ILD, including IPF.

The most robust efficacy response was observed in PH-ILD subjects who achieved doses greater than 9 breaths (Figure 1-1).

Figure 1-1 Forest Plot of Subgroup Analyses of Peak 6MWD at Week 16 in RIN-PH-201



Abbreviations: 6MWD, 6-Minute Walk Distance

A target dose of 12 breaths is further supported by the differences observed in FVC for those patients achieving the 9-breath target dose or greater in the INCREASE study. At Week 16, subjects achieving a dose of at least 9 breaths demonstrated a 47.5 mL placebo-corrected increase in FVC versus a 2.4 mL placebo-corrected increase in FVC for subjects whose doses were less than 9 breaths. There were no safety concerns noted with doses up to 12 breaths, and the safety profile of inhaled treprostinil in PH-ILD patients was consistent with previous studies in other patient populations.

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that inhaled treprostinil will have a positive effect on absolute FVC after 52 weeks of therapy as compared with placebo when administered to subjects with IPF.

2 PRIMARY OBJECTIVE

The primary objective of RIN-PF-301 is to evaluate the superiority of inhaled treprostinil against placebo for the change in absolute FVC from baseline to Week 52.

2.1 EFFICACY ENDPOINTS

2.1.1 Primary Endpoint

The primary endpoint is the change in absolute FVC in subjects with IPF from baseline to Week 52.

2.1.2 Secondary Endpoints

The secondary endpoints of this study evaluate the effect of inhaled treprostinil on the following parameters in subjects with IPF:

- Time to clinical worsening (including time to death, respiratory hospitalization, or ≥10% relative decline in % predicted FVC)
- Time to first acute exacerbation of IPF
- Overall survival at Week 52
- Change from baseline in % predicted FVC at Week 52
- Change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) score at Week 52
- Change from baseline in diffusion capacity of lungs for carbon monoxide (DLCO) at Week 52

2.1.3 Exploratory Endpoints

The exploratory endpoints of this study evaluate the effect of inhaled treprostinil on the following parameters in subjects with IPF:

- Change from baseline in absolute FVC at Weeks 16, 28, and 40
- Change from baseline in NT-proBNP at Week 52
- Change from baseline in resting supplemental oxygen use at Week 52
- Evaluation of pharmacogenomics and biomarkers for subjects who consent to collection

2.2 SAFETY ENDPOINTS

Safety will be assessed by reviewing the following parameters:

- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory parameters
- Vital signs, including resting saturation of peripheral capillary oxygenation (SpO_2)
- 12-lead electrocardiograms (ECGs)

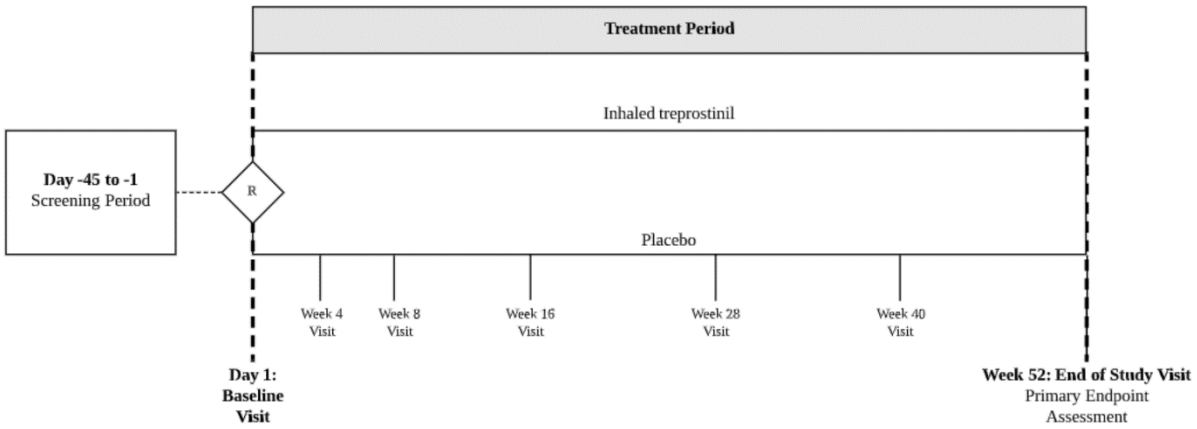
3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of subjects with IPF treated with inhaled treprostinil over a 52-week period.

Subject eligibility will be based on inclusion and exclusion criteria described in Section 4. Approximately 576 eligible subjects will be randomly assigned 1:1 to inhaled treprostinil or placebo at Baseline. Randomization will be stratified by IPF background therapy (nintedanib or pirfenidone vs no background therapy). All subjects will initiate inhaled treprostinil (6 mcg/breath) or placebo at a dose of 3 breaths (18 mcg) administered QID (during waking hours) and will titrate to a target dosing regimen of 12 breaths (72 mcg) QID.

Figure 3-1 RIN-PF-301 Study Design



Abbreviations: R, randomization

3.1.1 Study Entry (Screening and Baseline Visits)

Prospective subjects will be assessed during the Screening and Baseline Visits to determine eligibility for the study. Screening activities may occur up to 45 days before Baseline. At the start of Screening, subjects will sign the informed consent form (ICF), then undergo assessments as described in Table 3-1. Eligible subjects must have a diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu 2018) and confirmed by central review of HRCT imaging (performed within the previous 12 months) and surgical lung biopsy, if available. Confirmation that a subject qualifies must be received before the Baseline Visit and randomization.

All baseline assessments, including baseline spirometry (Table 3-1), must be completed and eligibility confirmed before subject randomization and administration of the first in-clinic dose of study drug. Eligible subjects will be randomly assigned to a treatment group via an interactive

voice/web response system (IXRS). Subjects will receive the first dose of study drug in the clinic followed by a 1-hour observation period. Study Day 1 is designated as the day the first dose of study drug is taken.

3.1.1.1 High-resolution Computed Tomography Scan

HRCT images must be transmitted for central review to confirm eligibility prior to the scheduled Baseline Visit; central review may take up to 7 business days. A HRCT scan may be performed during the Screening window if the subject did not have a scan in the previous 12 months. Confirmation that a subject qualifies from the central reviewer must be received before the Baseline Visit and randomization.

3.1.1.2 Surgical Lung Biopsy

If a surgical lung biopsy is available (ie, if histology was part of the diagnostic criteria per the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline, or performed for another reason), it should be sent for central review to confirm eligibility prior to the scheduled Baseline Visit; central review may take up to 7 business days. Confirmation that a subject qualifies from the central review must be received before the Baseline Visit and randomization.

3.1.2 Treatment Period

During the Treatment Period, 6 visits to the clinic will be required at Weeks 4, 8, 16, 28, 40, and 52. Visits will be scheduled to occur in accordance with the visit windows outlined in Table 3-1.

The order of study procedures will be scheduled taking into account the specific requirements outlined below.

- At study visits where the K-BILD is conducted, it must be completed before any of the other scheduled visit assessments are completed.
- Study drug will be dosed in-clinic at study visits during the Treatment Period. Subjects must bring their devices and study drug to clinic visits.
- Vital signs (including resting SpO_2) must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures will be performed during this 5-minute period, except the K-BILD if desired. When possible, vital signs should be collected prior to spirometry. If vital signs cannot be obtained prior to spirometry, they will be obtained after recovery from spirometry.
- Resting SpO_2 should be recorded using the same amount of supplemental oxygen (or room air) that was used at Baseline if at all possible.

- Spirometry must occur before DLCO, and after in-clinic dose of study drug during the Treatment Period. As best as possible, efforts should be made to schedule the assessment at approximately the same time of day at each study visit.
- DLCO measurements must be performed after the spirometry assessments. Efforts should be made to schedule the DLCO assessment at subsequent visits at approximately the same time of day.

Subjects will also be contacted by telephone or email at least weekly until Week 16 and monthly thereafter in between study visits to discuss study drug titration, assess study drug tolerability, monitor AEs, and document changes to concomitant medications. Email will not replace direct follow-up by telephone or in-clinic for clinically significant AEs or other emergent issues. All study contacts (eg, dosing instructions, AEs reported, medication changes) with the subject must be filed in the subject's study records. In the event that COVID-19-related restrictions prevent the conduct of in-person study visits, the Sponsor may direct sites to conduct a telehealth study visit in lieu of an in-clinic visit.

Subjects who discontinue study drug prematurely before Week 52 will be encouraged to remain in the study and attend the remaining scheduled study visits up to and including Week 52; a Premature Study Drug Discontinuation Visit should be conducted as soon as possible, and as best as possible prior to final dose of study drug.

In the event a subject withdraws from the study, an Early Termination (ET) Visit will be conducted; all assessments planned for the Week 52 Visit will be conducted during the ET Visit, as applicable. ET Visit assessments should be completed before the final dose of study drug if at all possible.

Subjects who complete the Week 52 Visit may be offered the opportunity to enter an OLE study after completing the final study visit.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Table 3-1 Overall Schedule of Times and Events

Assessment	Study Entry		Treatment Period						
Study Visit	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Week 16**	**Week 28**	**Week 40**	**Week 52 (EOS)**	**ET/PSDD Visit**
Visit Window (Days)	-45 to -1	1	29±5	57±5	113±5	196±7	280±7	365±7	
Informed consent	X								
Eligibility criteria	X	X							
Medical history with IPF history and demographics	X								
HRCT (performed if no scan within prior 12 months)	X								
HRCT submitted to central review[a]	X								
Surgical lung biopsy submitted to central review, if available[b]	X								
Physical examination	X					X		X	X
K-BILD[c]		X				X		X	X
Vital signs (including resting SpO_2)[d]	X	X	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP only)[e]	X	X	X	X	X	X	X	X	X
12-lead ECG[f]		X				X		X	X
Clinical laboratory assessments[g]	X	X	X	X	X	X	X	X	X
NT-proBNP		X			X	X	X	X	X
Blood sample for biomarkers[h]		X				X		X	X
Blood sample for whole genome sequencing[h]		X							
Documentation of resting supplemental O_2 use	X	X	X	X	X	X	X	X	X
Screening Spirometry (FVC, FEV_1)[i,j]	X								

Assessment	Study Entry		Treatment Period						
Study Visit	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Week 16**	**Week 28**	**Week 40**	**Week 52 (EOS)**	**ET/PSDD Visit**
Visit Window (Days)	-45 to -1	1	29±5	57±5	113±5	196±7	280±7	365±7	
Baseline spirometry (FVC; before randomization and before study drug dosing)[j]		X							
Treatment Period spirometry (FVC; after study drug dosing)[j]			X	X	X	X	X	X	X[n]
DLCO[k]		X				X		X	X
Randomization		X[l]							
Subject device training		X							
Dispense blinded study drug/dosing diary/review instructions		X	X	X	X	X	X		
In-clinic dosing of study drug		X[l]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[n]
1-hour post-dose observation period		X							
Return blinded study drug/review subject diary/perform accountability			X	X	X	X	X	X	X
Vital status[o]								X	X
Enrollment into OLE for continuing subjects								X	
Telephone/email contact (between visits)		◄——weekly until Week 16 and monthly thereafter——►							
Nonelective hospitalizations	◄——►								
Acute exacerbations of IPF	◄——►								
AE/SAE monitoring	◄——►								
Concomitant medications	◄——►								

Abbreviations: AE, adverse event; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; EOS, End of Study; ET, Early Termination; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; PSDD, premature study drug discontinuation; SAE, serious adverse event; SpO_2, saturation of peripheral capillary oxygenation; WOCBP, women of childbearing potential

a HRCT images must be transmitted for central review to confirm eligibility prior to the scheduled Baseline Visit (review may take up to 7 business days).

b Surgical lung biopsy, if available, should be submitted for central review to confirm eligibility prior to the scheduled Baseline Visit (review may take up to 7 business days).

c At study visits where the K-BILD is conducted, it must be completed before any of the other scheduled visit assessments are completed. When vital signs or ECGs are conducted as the second assessment during a study visit after the K-BILD, it is permitted for the subject to complete the K-BILD during the 5-minute rest period prior to vital signs or ECGs. The K-BILD will be completed by the subject on their own in a quiet area before any of the other scheduled visit assessments are completed. Site personnel should check the answers in the questionnaire for completeness.

d Vital signs (including blood pressure, heart rate, respiratory rate, temperature, weight, and resting SpO_2) must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. Height will be assessed at Screening only. No other measurements or procedures may be performed during this 5-minute rest period, with the exception of the K-BILD questionnaire if vital signs are performed as the second study assessment completed during applicable study visits. When possible, vital signs should be collected prior to spirometry. If vital signs cannot be obtained prior to spirometry, they will be obtained after recovery from spirometry. Resting SpO_2 should be recorded using the same amount of supplemental oxygen (or room air) that was used at Baseline, if at all possible.

e Urine dipstick pregnancy tests will be provided by the central laboratory and will be performed in all women of childbearing potential at every visit and, if necessary, at home or at a local laboratory/doctor between visits or if unable to make a visit in person.

f 12-lead ECGs will be recorded after at least 5 minutes of rest. No other measurements or procedures may be performed during this 5-minute period, with the exception of the K-BILD questionnaire if ECGs are performed as the second study assessment completed during applicable study visits.

g The results of all clinical laboratory tests conducted at Screening must be assessed by the Investigator to determine each subject's eligibility to participate in the study prior to starting study drug.

h For subjects who consent to collection.

i Spirometry results will be transmitted for central review to ensure the quality of the primary endpoint measurement and to confirm eligibility at Screening. The central spirometry review will provide feedback to the investigational site on the performance of the testing as needed. Central review of spirometry at Screening may take up to 2 business days.

j At each timepoint, spirometry will be performed with the subject in a seated position. Spirometry maneuvers will be repeated (up to 8 attempts) until 3 acceptable attempts have been completed. Efforts should be made to schedule the assessment at approximately the same time of day at each study visit. Subjects should refrain from strenuous activity for at least 12 hours and smoking for at least 30 minutes prior to testing. For subjects on bronchodilators, spirometry should be performed consistently throughout the study in relation to timing of bronchodilator administration. Spirometry must occur before DLCO. At Baseline, spirometry must occur before randomization and before administration of the first in-clinic dose of study drug. During the Treatment Period, spirometry will occur after the in-clinic dose of study drug.

k DLCO measurements must be performed after the spirometry assessments. Efforts should be made to schedule the DLCO assessment at subsequent visits at approximately the same time of day.

l All baseline assessments, including baseline spirometry, must be completed and eligibility confirmed before subject randomization and administration of the first in-clinic dose of study drug.

m Study drug will be dosed in-clinic at study visits during the Treatment Period. Subjects must bring their devices and study drug to clinic visits. Spirometry assessments will be scheduled to occur after the in-clinic dose of study drug during the Treatment Period.

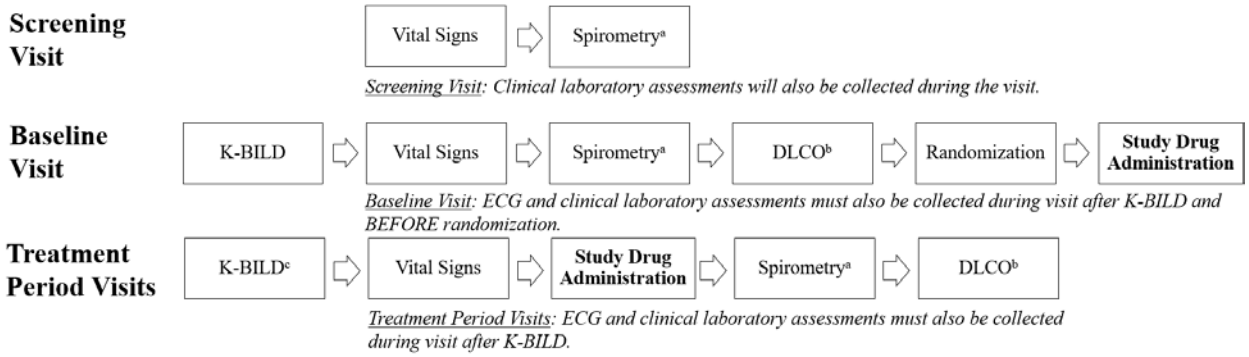
n Spirometry assessments should be performed prior to study drug discontinuation at the PSDD and/or ET Visits if at all possible.

o Every attempt will be made to assess vital status for all subjects at Week 52, including those who discontinue the study prematurely or who withdraw consent. Subjects who undergo lung transplantation will be censored as alive at the time of transplant.

3.3 CLINICAL ASSESSMENTS

All assessments will be performed according to the schedule outlined in Table 3-1. At all visits, procedures should be scheduled taking into account the order of procedures in Figure 3-2.

Figure 3-2 Order of Procedures



Abbreviations: DLCO, diffusion capacity of lungs for carbon monoxide; ECG, electrocardiogram; K-BILD, King's Brief Interstitial Lung Disease Questionnaire

a Efforts should be made to schedule spirometry at approximately the same time of day at each study visit. Subjects should refrain from strenuous activity for at least 12 hours and smoking for at least 30 minutes prior to testing.

b DLCO is not required at all Treatment Period visits. When required, efforts should be made to schedule the DLCO assessment at subsequent visits at approximately the same time of day.

c K-BILD is not required at all Treatment Period visits. When required, it should be completed first.

3.3.1 Efficacy Assessments

3.3.1.1 Spirometry

Spirometry will be performed using the SpiroSphere® spirometer provided by the Sponsor to all participating sites. Absolute and % predicted forced expiratory volume in 1 second (FEV_1) and FVC will be collected. At each timepoint, spirometry will be performed with the subject in a seated position. Spirometry maneuvers will be repeated (up to 8 attempts) until 3 acceptable attempts have been completed. If both pre- and post-bronchodilator testing is performed by the center, only the pre-bronchodilator values will be recorded for the purposes of the study. Efforts should be made to schedule the assessment at approximately the same time of day at each study visit. Subjects should refrain from strenuous activity for at least 12 hours and smoking for at least 30 minutes prior to testing. For subjects on bronchodilators, spirometry should be performed consistently throughout the study in relation to timing of bronchodilator administration. Spirometry must occur before DLCO. At Baseline, spirometry must occur before randomization and before administration of the first in-clinic dose of study drug. During the Treatment Period, spirometry will occur after the in-clinic dose of study drug. Spirometry

assessments should be performed prior to study drug discontinuation at the premature study drug discontinuation and/or ET Visits if at all possible.

Spirometry results will be transmitted for central review to ensure the quality of the primary endpoint measurement and to confirm eligibility at Screening. The central spirometry review will provide feedback to the investigational site on performance of the testing as needed. Central review of spirometry at Screening may take up to 2 business days.

Every effort should be made to perform the Week 52 Visit in the clinic for collection of spirometry. In the event a site is unable to perform in-clinic visits due to COVID-19-related restrictions for the Week 52 Visit or for an ET Visit, spirometry may be performed by qualified respiratory therapists/study personnel using the provided SpiroSphere spirometer at the subject's home with prior Sponsor approval.

3.3.1.2 Acute Exacerbations of Idiopathic Pulmonary Fibrosis

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

1. Previous or concurrent diagnosis of IPF
2. Acute worsening or development of dyspnea typically of less than 1-month duration
3. Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern
4. Deterioration not fully explained by cardiac failure or fluid overload

For the purposes of this protocol, events that are clinically considered to meet the definition of acute exacerbation must be reported for adjudication.

Exacerbations of IPF are to be recorded throughout the duration of the study from the time of informed consent until study termination. Exacerbations of IPF will also be reported as AEs or SAEs (see Appendix 15.1).

The analysis of acute exacerbations of IPF will be based on the Clinical Endpoint Committee's (CEC's) adjudication of exacerbations. Supportive documentation will be submitted by the

Investigator to aid in the CEC's adjudication of exacerbations. See Section 10.8 for additional information about the CEC.

3.3.1.3 Clinical Worsening

Clinical worsening is defined as the occurrence of any 1 of the following (morbidity or mortality) events and will be evaluated from the time of randomization until a subject terminates the study:

- Death (all causes)
- Hospitalization due to a respiratory indication
- ≥10% relative decline in % predicted FVC

Subjects experiencing a clinical worsening event may remain on study therapy for the duration of the study at the Investigator's discretion.

Supportive documentation will be submitted by the Investigator to aid in the CEC's adjudication. See Section 10.8 for additional information about the CEC.

3.3.1.3.1 Time to Respiratory-related Hospitalization

Nonelective hospitalizations will be recorded in the electronic Case Report Form (eCRF). The primary admission diagnosis will be collected and used to adjudicate respiratory-related hospitalizations. Time to nonelective respiratory-related hospitalization will be based on the date of hospitalization collected in the eCRF. AEs resulting in hospitalizations, regardless of cause or duration, must also be reported as SAEs per Section 9.1.2.

The analysis of time to respiratory-related hospitalization will be based on the adjudicated cause of hospitalization determined by the CEC. Supportive documentation will be submitted by the Investigator to aid in the CEC's adjudication of hospitalizations. See Section 10.8 for additional information about the CEC.

3.3.1.3.2 Time to Death and Time to Respiratory-related Death

Time to death will be based on the date of death captured in the eCRF or will be based on information obtained from the vital status assessment.

The analysis of time to respiratory-related death will be based on the adjudicated cause of death determined by the CEC. Supportive documentation will be submitted by the Investigator to aid in the CEC's adjudication of deaths. See Section 10.8 for additional information about the CEC.

3.3.1.4 King's Brief Interstitial Lung Disease Questionnaire

The K-BILD is a self-administered, 15-item questionnaire validated for patients with ILD consisting of 3 domains (breathlessness and activities, psychological, and chest symptoms) (Patel 2012). The K-BILD will be completed by the subject on their own in a quiet area before any of the other scheduled visit assessments are completed. The K-BILD may be conducted during the 5-minute rest period for vital signs or 12-lead ECGs when vital signs or ECGs are conducted as the second assessment during a study visit after the K-BILD. Site personnel should check the answers in the questionnaire for completeness.

3.3.1.5 Supplemental Oxygen Requirement

The amount of supplemental oxygen (L/min) required by the subject at rest will be recorded at each visit throughout the study.

3.3.1.6 N-Terminal Pro-brain Natriuretic Peptide

Plasma NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006).

3.3.1.7 Lung Diffusion Capacity

Measurement of absolute and % predicted DLCO (uncorrected for hemoglobin and lung volume) will be performed using a center's own equipment. If several devices are available at the site, the same equipment should be used to conduct study assessments at each measurement, if at all possible.

DLCO measurements must be performed after the spirometry assessments. Efforts should be made to schedule the DLCO assessment at subsequent visits at approximately the same time of day.

DLCO measurement data will be transmitted by the site to the designated central respiratory testing reader. The central review will provide feedback to the investigational site on performance of the testing as needed.

3.3.2 Safety Assessments

During this study, treatment-emergent changes in physical examination findings, vital signs, clinical laboratory parameters, ECG parameters, oxygenation parameters, pulmonary function, and the development of treatment-emergent AEs will be the primary assessments of safety. Hospitalizations due to respiratory indications, acute exacerbations of IPF, concomitant medications, and mortality data will be recorded from the time of informed consent until study termination (or ET for those subjects discontinuing the study prematurely).

3.3.2.1 Medical History and Physical Examination

A complete medical history, demographics, IPF history, and physical examination will be conducted during Screening. If any changes to the medical history occur between the Screening and Baseline Visit, they must be recorded. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs will be recorded. Physical examinations will also occur at Weeks 28 and 52 (or ET/premature study drug discontinuation) and must be conducted by appropriate study personnel as documented on the Delegation of Authority Log. Any significant changes to the subject's medical condition, such as new abnormal findings or worsening of conditions present at Baseline noted during subsequent physical examinations, must be documented throughout the course of the study and reported as AEs.

Race and ethnicity data will be collected in this study. This information is important to collect since, along with other demographic information like age and sex, these subject characteristics may influence responses to the study drug. In addition, this information is required to be collected by some regulatory agencies so that differences in responses to the study drug can be investigated appropriately (eg, US FDA). Study data will be summarized by these factors to provide a more thorough examination of potential factors underlying the safety, tolerability, and efficacy of the study drug.

3.3.2.2 Vital Signs

Vital signs measured will include blood pressure (systolic and diastolic), heart rate, respiratory rate, temperature, weight, and resting SpO_2. Height will be assessed at Screening only. Vital signs must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures may be performed during this 5-minute rest period, with the exception of the K-BILD questionnaire if vital signs are performed as the second study assessment completed during applicable study visits. When possible, vital signs should be collected prior to spirometry. If vital signs cannot be obtained prior to spirometry, they will be obtained after recovery from spirometry. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms. As best as possible, SpO_2 should be recorded using the same amount of oxygen (or room air) that was used at Baseline.

3.3.2.3 Clinical Laboratory Parameters

A Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited central laboratory will be used for laboratory analysis. The results of all clinical laboratory tests conducted at Screening must be assessed by the Investigator to determine each subject's eligibility to participate in the study prior to starting study drug.

Investigators will review all clinical laboratory test results, and for any results reported out of normal range, determine whether these values are in the context of expected fluctuations in the disease under study or in light of the subject's medical history (not clinically significant) or unexpected/unusual with respect to medical history or current health status (clinically significant), and record this in the source documentation. 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. Values for the following parameters will be obtained:

Table 3-2 Clinical Chemistry and Hematology Panels

Chemistry Panel	Hematology Panel
Sodium	Hemoglobin
Potassium	Hematocrit
Bicarbonate	Red blood cell count

Chemistry Panel	Hematology Panel
Chloride	White blood cell count
Total bilirubin	Platelet count
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	
Urea nitrogen	
Creatinine	
Calcium	
Albumin	

3.3.2.4 Urine Pregnancy Testing

Women of childbearing potential will undergo urine pregnancy testing. Urine dipstick pregnancy tests will be provided by the central laboratory and must be performed for all women of childbearing potential at every visit and, if necessary, at home or at a local laboratory/doctor between visits or if unable to make a visit in person. Use of local institutionally issued urine dipstick pregnancy tests or a blood test performed at the local laboratory are permitted if required by the institution. Subjects who become pregnant during the study will be discontinued from study drug and will be encouraged to remain in the study and attend the remaining scheduled study visits up to and including Week 52.

3.3.2.5 12-lead Electrocardiogram

A 12-lead ECG will be recorded after at least 5 minutes of rest using a center's own equipment. No other measurements or procedures may be performed during this 5-minute period, with the exception of the K-BILD questionnaire if ECGs are performed as the second study assessment completed during applicable study visits. Recordings will include lead II as a rhythm strip and contain at least 5 QRS complexes. ECG parameters to be collected include rhythm, heart rate, PR interval, QT interval, and QRS duration. Abnormalities must be documented, and clinical significance assessed by the Investigator.

3.3.2.6 Adverse Events and Serious Adverse Events

AEs will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, or until the subject withdraws consent and discontinues from the study, or until all Week 52 study assessments have been completed. Each

subject will be questioned for AEs at each scheduled study visit and during required telephone/email contacts. Subjects will also be instructed to spontaneously report all AEs throughout the study.

All AEs will be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for SAEs will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final study visit (Week 52 or ET as appropriate). All AEs/SAEs that occur while the subject is in the study will be recorded as instructed in this protocol. Sections 9 and 15.1 provide the guidelines and definitions for recording AEs.

3.3.2.7 Vital Status

Every attempt will be made to assess vital status for all subjects at Week 52, including those who discontinue the study prematurely or who withdraw consent. Subjects who undergo lung transplantation will be censored as alive at the time of transplant. The need for vital status information will be explained to subjects prior to their participation in the study. Subjects will be asked to consent to be contacted by site personnel, which could be by telephone calls, to allow collection of the vital status. If death occurs, the Investigator will review the circumstances, including the relevant medical records, to ascertain the cause of death. The cause of death will be adjudicated by the CEC. Collection of vital status will be performed in accordance with national ethical and regulatory guidelines.

3.3.3 Other Assessments

3.3.3.1 Biomarker Blood Sample

For subjects who consent to collection, biomarker samples will be shipped to the central laboratory for processing and storage prior to analysis. Subjects who do not wish to participate in the optional biomarker research may still participate in the clinical study.

3.3.3.2 Whole Genome Blood Sequencing

For subjects who consent to collection, blood samples will be shipped to the central laboratory for processing and storage until analysis. Whole genome sequences will be analyzed for genetic

markers that may be associated with clinical response and tolerability to prostacyclin therapy. Subjects who do not wish to participate in the optional genomic research may still participate in the clinical study.

3.3.3.3 Telephone/Email Contact

Subjects will be contacted by telephone or email at least weekly until Week 16 and monthly thereafter in-between study visits to discuss study drug titration, assess study drug tolerability, monitor AEs, and document changes to concomitant medications. Telephone/email contact may be replaced by a face-to-face interaction on the weeks where study visits occur if the information is obtained during the visit. The subject may be contacted via email in lieu of a telephone call; however, email will not replace direct follow-up by telephone or in-clinic for clinically significant AEs or other emergent issues. All study contacts (eg, dosing instructions, AEs reported, medication changes) with the subject must be noted in the source documentation.

In the event that COVID-19-related restrictions prevent the conduct of in-person study visits, the Sponsor may direct sites to conduct a telehealth study visit in lieu of an in-clinic visit and collect applicable information (ie, AEs/SAEs, concomitant medications, dosing information, etc). Dose titration should occur as appropriate.

3.4 NUMBER OF CENTERS

This study is multicenter with approximately 110 participating centers.

3.5 NUMBER OF SUBJECTS

The total sample size is planned to be approximately 576 subjects.

3.6 ESTIMATED STUDY DURATION

From Screening until completion of the study, the expected duration of study participation is approximately 58 weeks, including the 45-day Screening Period and a 52-week Treatment Period.

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during Screening and reconfirmed at Baseline prior to randomization and the first dose of study drug. If necessary, certain procedures may be

conducted during the Screening Period after obtaining informed consent to determine subject eligibility for the study. Confirmation that a subject qualifies from central review of the Screening spirometry, HRCT scan, and, if available, surgical lung biopsy must be received before the Baseline Visit and randomization.

4.1 INCLUSION CRITERIA

A subject is eligible for inclusion in this study if all the following criteria apply:

1. Subject gives voluntary informed consent to participate in the study.
2. Subject is ≥40 years of age, inclusive, at the time of signing informed consent.
3. The subject has a diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu 2018) and confirmed by central review of HRCT (performed within the previous 12 months) and if available, surgical lung biopsy. HRCT imaging must be "consistent with UIP," defined as meeting either criteria A, B, and C; or criteria A and C; or criteria B and C below:
   a. Subpleural and basal predominant honeycombing
   b. Subpleural and basal predominant reticular pattern with peripheral traction bronchiectasis or traction bronchiolectasis
   c. Absence of atypical features (eg, predominant ground-glass opacity, nodules, consolidation, etc). If ground-glass opacity is present, it must be less than the accompanying reticular pattern.

   Subjects with HRCT features deemed indeterminate for IPF (subpleural and basal predominant, subtle, reticulating pattern of fibrosis) may be considered for inclusion if coupled with a histopathological pattern of "UIP" or "probable UIP" on surgical lung biopsy and confirmed by central review.
4. FVC ≥45% predicted at Screening.
5. Subjects on pirfenidone or nintedanib must be on a stable and optimized dose for ≥30 days prior to Baseline. Concomitant use of both pirfenidone and nintedanib is not permitted.
6. Women of childbearing potential must be non-pregnant (as confirmed by a urine pregnancy test at Screening and Baseline) and non-lactating, and will do 1 of the following:
   a. Abstain from intercourse (when it is in line with their preferred and usual lifestyle)
   b. Use 2 medically acceptable, highly effective forms of contraception for the duration of the study, and at least 30 days after discontinuing study drug.

      Medically acceptable, highly effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable) and barrier methods (such as a condom or diaphragm) when used with a spermicide.

Women who are successfully sterilized (including hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or postmenopausal (defined as amenorrhea for at least 12 consecutive months) are not considered to be of reproductive potential.

7. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
8. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing, and likely to be cooperative with protocol requirements, including attending all study visits.

4.2 EXCLUSION CRITERIA

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

1. Subject is pregnant or lactating.
2. Subject has primary obstructive airway physiology: $FEV_1/FVC < 0.70$ at Screening.
3. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
4. The subject has received any PAH-approved therapy, including prostacyclin therapy (epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonists (selexipag), endothelin receptor antagonists, phosphodiesterase type 5 inhibitors (PDE5-Is), or soluble guanylate cyclase stimulators within 60 days prior to Baseline. As needed use of a PDE5-I for erectile dysfunction is permitted, provided no doses are taken within 48 hours of any study-related efficacy assessments.
5. Use of any of the following medications:
   a. Azathioprine (AZA), cyclosporine, mycophenolate mofetil, tacroliumus, oral corticosteroids (OCS) >20 mg/day or the combination of OCS+AZA+N-acetylcysteine within 30 days prior to Baseline.
   b. Cyclophosphamide within 60 days prior to Baseline
   c. Rituximab within 6 months prior to Baseline
6. The subject is receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
7. Exacerbation of IPF or active pulmonary or upper respiratory infection within 30 days prior to Baseline. Subjects must have completed any antibiotic or steroid regimens for treatment of the infection or acute exacerbation more than 30 days prior to Baseline to be eligible. If hospitalized for an acute exacerbation of IPF or a pulmonary or upper respiratory infection, subjects must have been discharged more than 90 days prior to Baseline to be eligible.
8. Uncontrolled cardiac disease, defined as myocardial infarction within 6 months prior to Baseline or unstable angina within 30 days prior to Baseline.
9. In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or would impair study participation or cooperation.

10. Use of any other investigational drug/device or participation in any investigational study in which the subject received a medical intervention (ie, procedure, device, medication/supplement) within 30 days prior to Screening. Subjects participating in non-interventional, observational, or registry studies are eligible.
11. Life expectancy <6 months due to IPF or a concomitant illness.
12. Acute pulmonary embolism within 90 days prior to Baseline.

4.3 PRESCRIBED THERAPY

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, will be recorded in the subject's source documents and transcribed into the eCRF as required. The flow rate of supplemental oxygen at rest will be recorded as outlined in Section 3.3.1.5.

Subjects must not be receiving prostacyclin therapy (epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonists (selexipag), endothelin receptor antagonists, PDE5-Is, or soluble guanylate cyclase stimulators within 60 days prior to Baseline through Week 52 or ET. As needed use of a PDE5-I for erectile dysfunction is permitted, provided no doses are taken within 48 hours of any study-related efficacy assessments.

Subjects on pirfenidone or nintedanib must be on a stable and optimized dose for ≥30 days prior to Baseline.

Additionally, use of any of the following chronic medications is prohibited:

- AZA, cyclosporine, mycophenolate mofetil, tacrolimus, OCS >20 mg/day or the combination of OCS+AZA+N-acetylcysteine within 30 days prior to Baseline through the Week 52 Visit
- Cyclophosphamide within 60 days prior to Baseline through the Week 52 Visit
- Rituximab within 6 months prior to Baseline through the Week 52 Visit

Subjects must have completed any antibiotic or steroid regimens for treatment of an acute exacerbation of IPF or active pulmonary or upper respiratory infection more than 30 days prior to Baseline to be eligible.

4.3.1 Management of Acute Exacerbations

In the event of an acute exacerbation, treatment should be according to Investigator discretion. All treatments considered necessary and adequate are allowed only for the acute time period associated with the exacerbation.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Subjects will be randomly assigned to inhaled treprostinil or placebo at Baseline.

5.2 RANDOMIZATION

Confirmation a subject qualifies based on Screening spirometry, HRCT parameters, and surgical lung biopsy (if available) must be received from the central reviewer before the Baseline Visit is conducted and randomization occurs. All baseline assessments, including spirometry, must be completed and eligibility confirmed before subject randomization administration of the first in-clinic dose of study drug. Subjects will be randomized 1:1 to inhaled treprostinil (6 mcg/breath) or placebo. An IXRS will be utilized for randomization. Randomization will occur using a centrally administered stratified permuted block randomization, stratified by IPF background therapy (nintedanib or pirfenidone vs no background therapy).

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

Study drug (treprostinil for inhalation solution or placebo) will be administered using the TD-300 ultrasonic nebulizer (Tyvaso Inhalation System®). Subjects will administer study drug in 4 separate treatment sessions each day during waking hours. Treatment sessions should be approximately 4 hours apart. Subjects will be trained on inhalation of study drug using the TD-300 ultrasonic nebulizer by the appropriate study site personnel. Subjects should follow the provided instructions, which include the commercially available Tyvaso Inhalation System Instructions for Use (IFU), for operation and daily cleaning of the device components.

Study drug (treprostinil inhalation solution, 0.6 mg/mL or placebo) is provided as clear liquid in 2.9-mL plastic ampules. One ampule contains a sufficient volume of study drug for all

4 treatment sessions in a single day. Any remaining study drug in the device medicine cup after the last treatment session will be discarded at the end of each day.

Dosing is based on the number of breaths administered in each treatment session. A single breath of treprostinil for inhalation solution via the TD-300 nebulizer delivers approximately 6 mcg of treprostinil.

6.1.1 Dose Titration

Subjects will be randomly assigned 1:1 to inhaled treprostinil or placebo at Baseline. All subjects will initiate study drug at a dose of 3 breaths (18 mcg) administered QID (during waking hours) and will titrate to a target dosing regimen of 12 breaths (72 mcg) QID. The first dose (3 breaths) of study drug will be administered in the clinic at the Baseline Visit after all assessments, including spirometry, have been performed, followed by at least a 1-hour observation period. Study drug will be administered at the subject's current dose in the clinic at all other study visits (Week 4 Visit until Week 52 Visit, unless the subject prematurely discontinues study drug). Study drug administration must occur before spirometry is performed during these study visits.

Study drug doses may be titrated up every 3 days, as tolerated, by administering an additional 1 breath (6 mcg) per treatment session, QID, until the target dose of 12 breaths QID is reached or the subject reaches their maximum clinically tolerated dose.

Table 6-1 serves as a guide for the recommended dose escalation schedule. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and clinical improvement. Dose increases should not occur more frequently than once every 3 days or be greater than a 1-breath increment. Each subject's dose should be maximized throughout the study. As needed, Investigators may extend the amount of time between dose increases (slow down titration) or decrease the dose during the study. Temporary interruption, dose decreases, and re-escalation of study drug are permitted. Subjects with hepatic insufficiency may have increased treprostinil exposure, which may lead to dose-dependent AEs. Investigators may consider alternate titration schedules in these subjects. Dosage adjustments

may be necessary if inhibitors or inducers of CYP2C8 (eg, gemfibrozil or rifampin) are added or withdrawn.

Table 6-1 Recommended Dose Escalation Schedule

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

Abbreviations: QID, 4 times daily

a Study day refers to the days on study drug, with the first dose of study drug being given on Day 1.

b If subjects are unable to tolerate the initial dose of 3 breaths, they may decrease their next dose to 1 or 2 breaths of study drug (as determined by the Investigator) QID (during waking hours). The subject will then gradually increase their dose to reach a minimum of 3 breaths and will continue titrating until the target dose of 12 breaths QID is reached or the subject reaches their maximum clinically tolerated dose.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject to monitor for AEs, clinical worsening events, and to make decisions about dose titration must be documented.

6.1.2 Premature Study Drug Discontinuation

Subjects who permanently discontinue study drug for any reason prior to reaching the Week 52 Visit will be asked to remain in the study and attend the remaining scheduled study visits up to and including Week 52. A Premature Study Drug Discontinuation Visit should be conducted as soon as possible, and prior to the final dose of study drug if at all possible.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, the Investigator, site personnel, subject, and Sponsor will remain blinded to the treatment assignment of all subjects. A medical emergency (eg, a life-threatening event) constitutes the only reason for unblinding during the study. Appropriate communication should take place between the site and the Sponsor (eg, Medical Monitor) before accessing the IXRS to

allow unblinding of a subject's treatment assignment if at all possible. However, the site may unblind without Sponsor communication if needed for subject safety.

6.3 COMPLIANCE

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. Site personnel will perform the following at all study visits:

- Ask the subject whether he or she has been compliant with dosing instructions.
- Collect and document all study drug returned by the subject (both number of used and unused ampules).
- Confirm study drug compliance by comparing the dosing instructions given to the subject since the previous study visit/subject study drug dosing diary and the amount of study drug returned.
- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

If it is determined that a subject is not compliant with study drug, site personnel must re-educate the subject on proper dosing compliance and its importance.

Subjects will be provided with a dosing diary to record dosing information from Baseline until Week 52. Subjects will be required to bring the completed dosing diary and return all study drug ampules (used and unused) at scheduled study visits. At each visit, all study drug (used and unused) will be returned by the subject and new study drug will be dispensed. Appropriate site personnel must document the number of used and unused ampules and determine if the appropriate amount of study drug remains based on the dose of study drug prescribed.

7 EXPERIMENTAL PROCEDURES

Assessments during the study will be performed according to Table 3-1. Every effort should be made to perform assessments as close as possible to the scheduled time points, within the visit window noted for each day on study as noted in Table 3-1, and the order of study procedures will be scheduled taking into account the specific requirements as noted in Figure 3-2. Assessment details are described in Sections 3.3.1, 3.3.2, and 3.3.3.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw consent from the study at any time.

If a subject discontinues from the study prematurely, the Investigator must provide an explanation in the eCRF and complete the End of Study Record for that subject. The Investigator should make every effort to perform ET evaluations prior to study discharge. If the subject is still on study drug, ET Visit assessments should be completed prior to the final dose of study drug if at all possible. AEs ongoing at the time of an ET Visit will be assessed as outlined in Section 9. Attempts to assess vital status will be made at 52 weeks after his/her randomization for subjects who have withdrawn from the study.

8.1.1 Lost to Follow-up

If a subject fails to return to the clinic or respond after at least 3 documented attempts by the site to contact the subject by telephone or email, the Investigator must issue a written letter by certified mail requesting the subject to contact the clinic or they may be withdrawn from the study. If no response to the certified letter is received, the subject will be considered lost to follow-up. The site will record the last date of contact in the eCRF as the termination date. Attempts to collect vital status will be made at Week 52.

8.1.2 Lung Transplantation

Subjects who undergo a lung transplant prior to Week 52 will be discontinued from the study. ET Visit assessments should be conducted prior to transplantation if at all possible. Subjects will be censored for vital status at the time of transplant.

8.2 CRITERIA FOR TERMINATING THE STUDY

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

8.3 CRITERIA FOR DISCONTINUING THE SITE

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

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

9 SAFETY REPORTING

All AEs/SAEs and product issues that occur while the subject is participating in the study will be documented as instructed per Section 9.2 and reported by the Investigator as instructed per Section 9.4.

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 to have a causal relationship with this treatment. An AE may include an intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. AEs may also include worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an AE.
- Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not AEs.
- Day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalizations for cosmetic elective surgery, social and/or convenience admissions).

9.1.2 Serious Adverse Event

An SAE is an AE occurring during the clinical study that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

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 drug 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. Life-threatening events often require interventions, such as emergency intubation, defibrillation, cardiopulmonary resuscitation, and other life-preserving measures. See Appendix 15.1 for further guidance on SAEs.

A significant disability/incapacity should be saved for AEs resulting in a substantial disruption of a person's ability to conduct normal life functions (ie, the AE resulted in a significant, persistent or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, and/or quality of life).

9.1.3 Product Complaint, Feedback, Inquiry

A product complaint is any written, electronic, or oral communication that alleges deficiencies of the identity, quality, durability, reliability, safety, effectiveness, or performance of a distributed device or drug product. This communication may reflect a complaint, feedback, or an inquiry about the device or drug product.

9.2 DOCUMENTATION OF ADVERSE EVENTS

All new AEs/SAEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject has withdrawn consent and discontinued from the study, or until all Week 52 Visit assessments have been completed.

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE, such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome, will be documented in the eCRF (see Section 9.1 and Appendix 15.1 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 will 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, for at least 30 days if the AE extends beyond the final visit, or until the subject withdraws consent. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up, even if they are ongoing more than 30 days after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages must be updated with any new or additional information as appropriate.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

Sites must enter initial or follow-up SAE information regardless of causality or expectedness into the Sponsor's Electronic Data Capture (EDC) system within 24 hours of awareness of an SAE. If a site is unable to enter the SAE electronically into the EDC system, it will utilize an alternative method for SAE reporting via submission of a scanned copy of the paper SAE Notification Report Form via email to [redacted] or fax at [redacted] within 24 hours of awareness. If the paper SAE Notification Report Form is submitted, the site will also be required to enter the SAE data into the EDC system. SAE source documents (eg,

hospital discharge summary or death certificate) will be submitted by the site via the EDC system (preferred method) or email to drugsafety@unither.com. 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 IRB/IEC/local equivalent body notification and receipt will be kept in the Clinical Investigator's study file.

9.4.1 Device Issue Reporting

Sites must document if an inhalation device is defective or suspected to be defective in the Sponsor's EDC System within 24 hours of awareness of a device deficiency. If a site is unable to enter the device deficiency electronically into the EDC system (eg, if the system is unavailable due to internet/login issues/upgrading), the site will utilize an alternative method for device deficiency reporting, ie, submission of the completed paper Clinical Trial Product Complaint Report Form via email to [redacted] or fax to [redacted] within 24 hours of awareness. If the paper Clinical Trial Product Complaint Report Form is submitted, the site will also be required to enter the device deficiency into the EDC system when available. The site should follow any additional instructions provided by the Sponsor to facilitate device replacement and return as needed during the study.

9.4.2 Study Drug Product Issue Reporting

Sites must document if study drug is defective or suspected to be defective (eg, discolored, damaged) in the Sponsor's EDC system within 24 hours of awareness. If a site is unable to enter the issue electronically into the EDC system (eg, if the system is unavailable due to internet/login issues/upgrading), the site will utilize an alternative method for study drug product issue reporting, ie, submission of the completed paper Clinical Trial Product Complaint Report Form via email to [redacted] or fax to [redacted] within 24 hours of awareness. If the paper Clinical Trial Product Complaint Report Form is submitted, the site will also be required to enter the device deficiency into the EDC system when available. The site should follow any additional instructions provided by the Sponsor to facilitate study drug replacement and return as needed during the study.

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 IEC in accordance with applicable national regulations and guidelines set forth by the IRB or IEC.

9.6 PREGNANCY

All subjects must be instructed to contact the Investigator immediately if they suspect they might be pregnant while participating in this study. Any pregnancy that occurs during study participation must be reported to the Sponsor via e-mail or fax [redacted], respectively) using the Pregnancy Notification and Outcome Form within 24 hours of learning of its occurrence. All pregnancies must be followed to determine outcome. A pregnancy is not an AE/SAE. If there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring, the pregnancy outcome becomes an AE/SAE. The United Therapeutics Global Product Safety and Pharmacovigilance department will follow up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification and Outcome Form.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion, or study discontinuation for any reason. A representative from the Sponsor or designee will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality-assured computerized database. Data clarifications will be generated, and the database will be edited as appropriate. The eCRF screens are to be reviewed periodically by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify his/her approval of the data. The Investigator will be required to re-sign a subject's eCRF if changes are made by the site after the Investigator signature has occurred. The database will be final when

all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

A sample size of 472 subjects will have at least 80% power to detect a difference in means of 80 mL in change from baseline in absolute FVC, assuming that the common standard deviation is 300 mL using a 2-group t-test with a 0.05 two-sided significance level. Assuming an 18% dropout rate, 576 subjects need to be randomized.

The assumptions related to sample size may be evaluated by review of blinded FVC data throughout the study and, if necessary, sample size will be recalculated.

10.3 ANALYSIS PLAN

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

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

10.3.1 Primary Estimand

RIN-PF-301 will compare inhaled treprostinil with placebo in subjects with IPF, with randomization stratified by IPF background therapy (nintedanib or pirfenidone vs no background therapy). The primary objective of RIN-PF-301 is to evaluate the superiority of inhaled

treprostinil against placebo for the change in absolute FVC from baseline to Week 52. The treatment effect of primary interest is for randomized and treated subjects, regardless of the extent of treatment adherence or early study treatment discontinuation but excluding the effects of lung transplantation. All available data, including post-treatment discontinuation data for subjects who prematurely discontinued treatment, will be used for primary analyses.

The intercurrent events that may affect the interpretation of the study results include early study treatment discontinuation (eg, due to AEs, lost to follow-up, physician decision, protocol violation, withdrawal by subject), initiation or change of IPF background therapy during the study, lung transplantation, and death. Subjects who discontinue study treatment prematurely are encouraged to remain in the study and continue their clinical visits until Week 52. The strategy for handling different intercurrent events including death will be specified in the SAP.

10.3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in absolute FVC in subjects with IPF from baseline to Week 52. This study hypothesizes that inhaled treprostinil will have a positive effect on absolute FVC after 52 weeks of therapy as compared with placebo when administered to subjects with IPF. For the primary analysis, the primary efficacy endpoint will be analyzed using MMRM, including baseline FVC and background therapy as covariates. If the assumptions for the parametric MMRM model are violated, an alternative non-parametric method will be used for primary analyses. All available data, including visits done after premature treatment withdrawal, will be used. Diagnoses of MMRM model, sensitivity analyses for the primary efficacy endpoint, and investigation of the effect of missing data on the primary endpoint will be specified in the SAP.

10.3.3 Secondary Efficacy Endpoints

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

- Time to clinical worsening (including time to death, respiratory hospitalization, or ≥10% relative decline in % predicted FVC)
- Time to first acute exacerbation of IPF
- Overall survival at Week 52

- Change from baseline in % predicted FVC at Week 52
- Change from baseline in K-BILD score at Week 52
- Change from baseline in DLCO at Week 52

For time to event endpoints (clinical worsening and acute exacerbation), Kaplan-Meier estimates will be calculated, and log-rank tests will be used to compare treatments. A similar approach to the analysis of the primary efficacy endpoint will be used for change in % predicted FVC and change in K-BILD score.

Multiplicity will be handled by a hierarchical testing approach with further details contained in the SAP. If the primary efficacy endpoint is statistically significant at an alpha level of 0.05, the secondary efficacy endpoints will be tested in a fixed sequence, as listed above. Testing will proceed only if the preceding test is statistically significant at an alpha level of 0.05.

10.3.4 Exploratory Endpoints

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

- Change from baseline in absolute FVC at Weeks 16, 28, and 40
- Change from baseline in NT-proBNP at Week 52
- Change from baseline in resting supplemental oxygen use at Week 52
- Evaluation of pharmacogenomics and biomarkers for subjects who consent to collection

A similar approach to the analysis of the primary efficacy endpoint will be used for the exploratory endpoints. No adjustment for multiplicity is planned.

10.3.5 Safety Analyses

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

- AEs and SAEs
- Clinical laboratory parameters
- Vital signs, including resting SpO_2
- 12-lead ECGs

All AEs as recorded by the Investigators will be assigned a Medical Dictionary for Regulatory Activities Preferred Term and System Organ Class by the Sponsor for reporting purposes. The

summary of AEs will include the number of subjects and incidence of AEs, as well as the risk difference of AEs and its confidence interval 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 vital signs, ECGs, and clinical laboratory parameters will be summarized by treatment group. No inferential analyses are planned on these safety endpoints.

10.4 INTERIM ANALYSIS

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

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

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

10.7 DATA MONITORING COMMITTEE

An independent external DMC will be established for the study and will include physicians knowledgeable in the treatment of IPF. Throughout the course of the study, the DMC will meet on a regular basis to monitor safety. Meetings will occur as outlined in the DMC Charter. The DMC 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 DMC as defined in the DMC Charter. The Sponsor will not have access to unblinded study data during this process.

10.8 CLINICAL ENDPOINT COMMITTEE

An independent CEC will be utilized during this study to adjudicate respiratory-related hospitalizations, acute exacerbations of IPF, and deaths on an ongoing basis. The CEC will be composed of clinicians who are not participating study Investigators. The independent CEC will review and confirm all specified events in a blinded fashion throughout the conduct of the study in accordance with the established charter.

Final adjudication of events will be reviewed and certified by the blinded CEC at the conclusion of the study.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

11.1.1 Study Drug

The Sponsor will supply study medication (treprostinil inhalation solution, 0.6 mg/mL or placebo), as clear liquid in 2.9-mL plastic ampules. The ampules will be packaged in sealed foil laminate pouches in groups of 4 ampules/pouch. Study drug cartons will be packaged containing the appropriate quantity of foil pouches for the study visit windows.

11.1.2 Study Device and Supplies

Treprostinil solution for inhalation is administered via an ultrasonic nebulizer. The Sponsor will supply commercially available TD-300 nebulizers (Tyvaso Inhalation System) to the site in standard packaging separate from study drug. Each Tyvaso Inhalation System device starter kit contains 2 nebulizers and a month's supply of accessories (disposable filters and plastic mouthpiece assembly, etc). The inhalation device starter kit will include the commercially available Tyvaso Inhalation IFU manual. Accessory kits will be provided at each dispensation visit starting at Week 4, and they will contain a month's supply of accessories (replacement disposable filters and a plastic mouthpiece assembly).

11.2 LABELING

11.2.1 Study Drug

Study drug will be labeled in a blinded fashion. The foil pouch and the outer study drug carton will each be labeled at a minimum with the study number, kit identification number (all foil

pouches within an individual study carton will contain the matching unique carton number), expiry date, Sponsor's name and address, and storage information (subject to regulatory requirements in each study region or country). Individual ampules within the foil pouches will be labeled with blinded lot identification and a statement identifying "For Clinical Trial Use Only".

11.2.2 Study Device and Supplies

Each Tyvaso Inhalation System device starter kit and accessory kit will be supplied using standard commercial packaging labeled at minimum with the study number, a kit identification number, and a "Do Not Dispense Beyond" or expiration date.

11.3 STORAGE AND HANDLING OF CLINICAL STUDY MATERIAL

11.3.1 Study Drug

Study drug will be stored at room temperature, 25ºC (77ºF), with excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Study drug will not be frozen, refrigerated, or exposed to heat. Ampules should be stored in the foil pouch to protect them from light. Once the foil pouch is opened, use ampules within 7 days.

Study drug will be stored in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access must be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study drug to any individual not participating in this clinical study.

11.3.2 Study Device and Supplies

Tyvaso Inhalation System device starter kit and accessory kits will be stored at 15ºC to 30ºC (59ºF to 86ºF) in a securely locked cabinet or enclosure with appropriate temperature monitoring. They will not be frozen, refrigerated, or exposed to heat. Access must be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study devices or supplies to any individual not participating in this clinical study.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

11.4.1 Study Drug

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. Additional shipments of study drug to the investigational center will be managed through the IXRS commensurate with the number of subjects enrolled.

At Baseline, an IXRS will be utilized to randomize qualifying subjects into the respective treatment groups and assign the appropriate study drug carton for the first 4-week treatment interval. Site personnel will register each subsequent study visit in the IXRS and obtain study drug cartons assigned to the subjects based upon their current treatment allocation. All study drug previously dispensed to a subject, including all used and unused ampules, should be returned to the study site at subsequent study visits.

In the event a subject is unable to return to the clinic due to COVID-19-related restrictions, direct shipment of study drug and devices to subjects may be considered in certain circumstances with prior Sponsor approval.

11.4.2 Study Device and Supplies

Study sites will be supplied with a sufficient quantity of Tyvaso Inhalation System device starter kits and accessory kits to begin enrollment in the study. Additional shipments of device starter and accessory kits to the investigational center will be managed through the IXRS commensurate with the number of subjects enrolled.

Each subject will be dispensed a Tyvaso Inhalation System device starter kit containing 2 nebulizers at the time of randomization by the IXRS. The IXRS will also dispense the appropriate number of accessory kits for the next visit window interval when a study visit is registered.

Subjects will continue to use their devices throughout the duration of the study. Nebulizer devices may be used by a subject for up to 2 years from the date the Tyvaso Inhalation System device starter kit was dispensed. In the event a device malfunction occurs during the study, a new device starter kit will be dispensed to a subject. If a device malfunction occurs, site

personnel will notify the Sponsor and follow the instructions provided regarding documentation of the malfunction and return of the device.

Nebulizers used during the study will be collected from subjects upon premature study drug discontinuation or early termination, at the Week 52 visit if the subject does not enroll into the RIN-PF-302 OLE study, or at the time of replacement in the event of device malfunction. Nebulizers will be returned to a Sponsor-designated location for destruction or evaluation.

Subjects may dispose of the used filters and plastic mouthpiece assembly contained in the accessory kits in their normal household waste and do not need to return those used supplies to the investigational center.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per-subject basis. Drug accountability records are to be maintained during the study, including, but not limited to, the study drug cartons received from the Sponsor, the cartons dispensed to each subject, and the quantity of used/unused study drug ampules returned to the site by the subject. Any discrepancies must be accounted for and documented.

Once a representative from the Sponsor is able to confirm study drug accountability records, study drug will be returned to a Sponsor-designated location for destruction and/or destroyed onsite per institutional policy if confirmed by the Sponsor.

Accountability records of the Tyvaso Inhalation System device starter kits issued to the site and the nebulizers dispensed to/returned from subjects will be maintained during the study. Once a representative from the Sponsor is able to confirm device accountability records, nebulizers will be returned to a Sponsor-designated location.

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) and GCP guidelines and all applicable national regulations. The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the

study, an annual safety report will be compiled by the Sponsor for submission to those regulatory authorities and IRBs/IECs that require it. Any additional national reporting requirements specified by the applicable regulations, regulatory authorities, or IRB/EC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks, and all study procedures to the subject. The subject must sign and date an IRB/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.

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 with a copy of the approval letter. The IRB/IEC must also review and approve the study site's ICF and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/EC prior to the start of the study.

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

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/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's 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, at a minimum, the following documents will be provided to the site: Investigator's Brochure, clinical study protocol, ICF, Budget Agreement, and access to the eCRF.

At a minimum, the site will be required to provide the following documents to UTC or designee prior to study start: Signature page of the protocol, Form FDA 1572 (as per local regulations), Financial Disclosure Form(s), IRB/IEC Composition and Roster, IRB/IEC protocol and ICF 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, 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 the subject's 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.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially 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 or its designee 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, 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 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 will periodically contact the site and conduct monitoring visits (on-site or remotely). During these visits, the Monitor will at a minimum confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

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

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15 APPENDICES

15.1 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

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

"How are you doing (feeling)?"

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

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

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

Using provided definitions, the Investigator will then:

1. Rate the intensity and seriousness of the AE
2. Estimate the causality of the AE to study drug, and
3. Note actions taken to counteract the AE.

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

INTENSITY

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

Definitions of the intensity categories are as follows:

- Mild: discomfort noted but no disruption to normal daily activities
- Moderate: discomfort sufficient to disrupt normal daily activities
- Severe: inability to work or perform normal daily activities

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

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

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (eg, hospitalization for a routine right heart catheterization).
- Treatment that was elective or pre-planned for a pre-existing condition not associated with any deterioration in condition (eg, pre-planned operation that 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, concurrent disease and the AE, 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 AE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the AE, 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 AE. The event responds to dechallenge - the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
  - Has a reasonable temporal relationship to study drug
  - The event has a plausible biologic link to the activity of the study drug
  - Not readily explained by an intercurrent illness
  - Not readily explained by external event
  - Improves on discontinuation of study drug
  - If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose or regimen of the study drug was not changed.
- Dose Increased – The dose or regimen of study drug was increased.
- Dose Decreased – The dose or regimen of study drug was decreased.
- Drug Interrupted – Administration of the study drug was stopped temporarily.
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted.
- Unknown – Changes to the administration of the study drug cannot be determined.
- Not Applicable

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

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/are residual sequela(e). 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.

15.2 IPF DIAGNOSTIC CRITERIA

To be eligible for the study, subjects must have a diagnosis of IPF based on the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu 2018) and confirmed by central review of HRCT (performed within the previous 12 months) and if available, surgical lung biopsy. HRCT imaging must be "consistent with UIP," defined as meeting either criteria A, B, and C; or criteria A and C; or criteria B and C below:

a. Subpleural and basal predominant honeycombing
b. Subpleural and basal predominant reticular pattern with peripheral traction bronchiectasis or traction bronchiolectasis
c. Absence of atypical features (eg, predominant ground-glass opacity, nodules, consolidation, etc). If ground-glass opacity is present, it must be less than the accompanying reticular pattern.

Subjects with HRCT features deemed indeterminate for IPF (subpleural and basal predominant, subtle, reticulating pattern of fibrosis) may be considered for inclusion if coupled with a histopathological pattern of "UIP" or "probable UIP" on surgical lung biopsy and confirmed by central review.

In the instances where a surgical lung biopsy was performed, it should be sent for central review. Table 15-1 summarizes eligible and ineligible combinations of HRCT and histopathology patterns for the study.

Table 15-1 High-resolution Computed Tomography and Histopathology Patterns

		Histopathology Pattern				
		No Biopsy Available	**UIP**	**Probable UIP**	**Indeterminate for UIP**	**Alternative Diagnosis**
HRCT Pattern	**UIP**	Eligible	Eligible	Eligible	Eligible	Not eligible
	Probable UIP	Eligible	Eligible	Eligible	Eligible	Not eligible
	Indeterminate for UIP	Not eligible	Eligible	Eligible	Not eligible	Not eligible
	Alternative Diagnosis	Not eligible	Not eligible	Not eligible	Not eligible	Not eligible

Abbreviations: HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia
Source: adapted from 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu 2018).