A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease

TRAIL1

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LIST OF ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvate transaminase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
bFGF	basic fibroblast growth factor
CI	confidence interval
CRF	case report form
D-12	Dyspnea 12 questionnaire
DCC	Data Coordinating Center
DL_{CO}	carbon monoxide diffusing capacity
% DL_{CO}	percent predicted carbon monoxide diffusing capacity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
ERS	European Respiratory Society
FDA	(United States) Food and Drug Administration
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
%FVC	percent predicted forced vital capacity
GGT	gamma-glutamyl transferase
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
HRQOL	Health Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IND	Investigational New Drug
IPF	idiopathic pulmonary
IRB	Institutional Review Board
ITT	intent-to-treat
L	liter
LCQ	Leicester Cough Questionnaire
LDH	lactic dehydrogenase
L/min	liters per minute
MedDRA	Medical Dictionary for Regulatory Activities
m	meter
MAC	Mortality Assessment Committee
mg	Milligram
mg/d	milligrams per day
mL	Milliliter
mm Hg	millimeters of mercury
msec	Millisecond
NIH	National Institutes of Health

PaO2	partial pressure of oxygen
PDGF	platelet-derived growth
PF	pulmonary fibrosis
PFS	progression-free survival
PFT	pulmonary function test
QT interval	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart-rate–corrected QT interval
RA	rheumatoid arthritis
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
SLB	surgical lung biopsy
SmPC	Summary of Product Characteristics
SP2	Shionogi Phase 2 study
SP3	Shionogi Phase 3 study
SpO2	oxygen saturation by pulse oximetry
Study treatment	pirfenidone or placebo equivalent
SPF	sun protection factor
TLCO	carbon monoxide transfer capacity
TID	three times per day
UIP	usual interstitial pneumonia
ULN	upper limit of normal
USP	United States Pharmacopeia
UV-A	ultraviolet A (radiation)
wk	Week
Sponsor	Brigham and Women's Hospital, Boston, MA
Financial Support provided by	Genentech, Inc / Roche

STATEMENT OF COMPLIANCE

This trial will be conducted with Good Clinical Practice (GCP) and in accordance with the Code of Federal Regulations on the Protection of Human Subjects (21 CFR Part 50). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the applicable Institutional Review Boards (IRBs), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
(Print/Type Name)

Signed: _____
(Signature)

Date: _____
(MM/DD/YYYY)

PROTOCOL SUMMARY

Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease
Précis:	A Phase 2, randomized, double blind, placebo controlled clinical trial designed to evaluate the efficacy and safety of administering pirfenidone or placebo for 52 weeks to subjects with RA-ILD. Patients meeting the eligibility criteria for the study will be randomized to receive either pirfenidone 2403 mg/d or placebo. Efficacy will be evaluated through interval testing of pulmonary function tests, patient reported outcomes, adverse events and survival. Safety will be assessed by determining differences between the treatment arms for the rate of adverse events, serious adverse events, rates of acute exacerbation, hospitalization and all-cause mortality.
Objectives:	To assess the efficacy and safety of pirfenidone 2403 mg/day as compared to placebo in patients with RA-associated interstitial lung disease. To explore the role of peripheral blood biomarkers in predicting disease progression and survival in patients with RA-associated interstitial lung disease. To explore a spectrum of validated questionnaires to assess disease specific PROs including overall health, and perspectives on symptoms, performance and quality of life.
Endpoints	**Primary Endpoint:** Incidence of the composite endpoint of decline from baseline in percent predicted FVC of 10% or greater or death during the study period. **Pre-Specified Secondary Endpoints:** 1. Incidence of the composite endpoint of decline from baseline in percent predicted FVC of 10% or greater during the study period 2. Frequency of progressive disease as defined by OMERACT: Relative decline from baseline in percent predicted FVC of ≥10%, or relative change from baseline in percent predicted FVC ≥ 5% and < 10%, and ≥15% relative DL_{CO} (Khanna, Mittoo et al. 2015) 3. Change from baseline to end of study in absolute value of FVC 4. Change from baseline to end of study of percent predicted FVC 5. Slope of percent predicted FVC over study period 6. Slope of absolute FVC over study period 7. Time to decline of 10% or greater in percent predicted FVC ordeath over study period 8. Proportion of participants with all-cause mortality 9. Proportion of participants with all-cause hospitalization

	10. Proportion of participants with hospitalization for respiratory cause 11. Number of respiratory exacerbations requiring hospitalizations 12. Proportion of participants with and number of treatment-emergent AEs 13. Proportion of participants with and number of treatment-emergent serious adverse events (SAEs) 14. Proportion of participants with and number of treatment-emergent/treatment-related AEs 15. Proportion of participants with and number of treatment-emergent/treatment-related SAEs 16. Proportion of participants with and number of AEs leading to early discontinuation of study treatment 17. Proportion of participants with and number of treatment-emergent death or transplant 18. Proportion of participants with and number of treatment-emergent RA-ILD-related mortality 19. Change from Baseline to end of study in dyspnea, as measured by the Dyspnea 12 questionnaire **Exploratory:** 1. Change from Baseline to end of study in Disease Activity Score (DAS) and RAPID3 score (RA disease activity score) 2. Change from Baseline to end of study in Routine Assessment of Patient Index Data 3 (RAPID3) score (RA disease activity score) 3. Change from Baseline to end of study in Erythrocyte Sedimentation Rate (ESR) 4. Change from Baseline to end of study in C-Reactive Protein (CRP) 5. Candidate biomarker expression in the peripheral blood of patients with RA-ILD over the study period of treatment and the study follow-up period 6. Changes from Baseline to end of study in HRCT parameters evaluated by quantitative functional imaging 7. Changes from Baseline to Week 13, 26, 39 and 52 in the St. George's Respiratory Questionnaire (SGRQ) 8. Changes from Baseline to Week 13, 26 and 39 in Dyspnea 12 questionnaire 9. Changes from Baseline to Week 13, 26, 39 and 52 in Leicester Cough Questionnaire (LCQ) 10. Changes from Baseline to Week 13, 26, 39 and 52 in the Patient global assessment 11. Changes from Baseline to Week 13, 26, 39 and 52 in the Health assessment questionnaire
Population:	Approximately 270 randomized participants from recruitment sites in the United States, Canada, the United Kingdom and Australia, including both male and female patients aged 18-85 years, diagnosed with RA (according to revised 2010 ACR/EULAR criteria) and ILD (supported by clinically

	indicated HRCT), without evidence or suspicion of an alternative diagnosis that may contribute to their interstitial lung disease. They must also meet all other inclusion and exclusion criteria as detailed below.
Phase:	Phase II
Number of Sites enrolling participants:	approximately 33
Description of Study Agents:	Study treatment is defined as either pirfenidone 2403 mg/d or placebo equivalent administered in divided doses three times per day (TID). Study treatment should be titrated over 14 days, as tolerated, to the full dose of 9 capsules per day (three capsules TID), as follows: • Days 1–7: one capsule TID • Days 8–14: two capsules TID • Days 15-21: three capsules TID (maximum of 9 capsules daily) Participants will remain on a stable maintenance dose for the duration of the study period (Day 22 to Week 52) unless the dose is reduced to manage an AE. Genentech will supply all study medications (pirfenidone and matching placebo). There will be 270 capsules per bottle, which will be labeled for investigational use only. Pirfenidone 267-mg and placebo will be supplied in opaque, hard, white gelatin capsules that are visually indistinguishable.
Study Duration:	Approximately 4 years total study duration, sub-divided into the following components: - 30 month enrollment period - 12 month randomized, double-blind treatment period per patient - 1 month follow-up period after completion of drug therapy
Participant Duration:	Approximately 15 months: - screening = 1-2 months - treatment period = 12 months - follow-up after completion of study treatment = 1 month
Inclusion Criteria:	1. Age 18 through 85 years, inclusive, at Screening 2. Probable or definite diagnosis of RA according to revised 2010 ACR/EULAR criteria, without evidence or suspicion of an alternative diagnosis that may contribute to their interstitial lung disease. 3. Diagnosis of ILD a. supported by clinically indicated HRCT, and when available surgical lung biopsy (SLB), prior to Screening, and b. presence of fibrotic abnormality affecting more than 10% of the lung parenchyma, with or without traction bronchiectasis or honeycombing, on Screening and confirmed by adjudicated HRCT prior to Baseline

	4. No features supporting an alternative diagnosis on transbronchial biopsy, or SLB, if performed prior to Screening 5. Attainment of the following centralized spirometry criteria (based on local spirometry on standardized equipment and centralized quality controlled): a. percent predicted FVC ≥ 40% at Screening b. change in pre-bronchodilator FVC (measured in liters) between Screening (Visit 1) and Baseline (Visit 2) must be a <10% relative difference, calculated as: 100% * [absolute value (Screening FVC – Baseline FVC) / Screening FVC] c. percent predicted DL_{CO} or TLCO ≥ 25% at Screening d. Screening (Visit 1) pre-bronchodilator(BD) and Post-BD spirometry meets ATS quality criteria as determined by a central reviewer e. Baseline (Visit 2) Pre-BD spirometry meets ATS quality criteria as determined by either a site Investigator or the central reviewer 6. Able to understand and sign a written informed consent form 7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of <1% per year, during the 52 week treatment period and for at least 118 days after the last dose of study drug. a. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). b. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. 8. For men who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below: a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 118 days after the last dose of study drug. b. Men must refrain from donating sperm during this same period.

Exclusion Criteria:	1. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator 2. Cigarette smoking or vaping within 3 months of Screening or unwilling to avoid tobacco products throughout the study 3. History of clinically significant environmental exposure known to cause pulmonary fibrosis (PF), including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds 4. Concurrent presence of the following conditions: a. Other interstitial lung disease, related to but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, or bronchiolitis obliterans organizing pneumonia b. Medical history including Human Immunodeficiency Virus (HIV) c. Medical history of viral hepatitis (positive Hep A antibody in the absence of elevated liver enzymes is not an exclusion) 5. Concurrent presence of other pleuropulmonary manifestations of RA, including but not limited to rheumatoid nodular disease of the lung, pleuritis/pleural thickening, and obliterative bronchiolitis 6. Post-bronchodilator FEV1/FVC <0.65 at Screening 7. Presence of pleural effusion occupying more than 20% of the hemithorax on Screening HRCT 8. Clinical diagnosis of a second connective tissue disease or overlap syndrome (including but not limited to scleroderma, Sjogren's polymyositis/dermatomyositis, systemic lupus erythematosus but excluding Raynaud's phenomena) 9. Coexistent clinically significant COPD/emphysema or asthma in the opinion of the site principle investigator 10. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis. The infection should be resolved per PI assessment prior to enrollment. Any use of antibiotics must be completed 2 weeks prior to the screening visit. Note that prophylactic antibiotics are not contraindicated or exclusionary 11. Any history of malignancy diagnosed within 5 years of screening, other than basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or low grade cervical carcinoma, and/or low grade prostate cancer. Criteria for low grade prostate cancer: • Patients with suspicion for prostate cancer based on PSA and/or DRE should have been evaluated by urology • Patients with NCCN very low risk prostate cancer (· T1c and Grade Group 1 (Gleason 6) and PSA <10 ng/mL and Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/coreg and · PSA density <0.15 ng/mL/g) can be monitored without intervention and enrolled in study

	• Patients with NCCN low risk prostate cancer can be monitored on a case by case basis (T1-T2a and Grade Group 1 (Gleason 6) and · PSA <10 ng/mL) and enrolled in study. • All other patients should be excluded. 12. History of LFT abnormalities as outlined below, or imaging, laboratory or other clinical information suggesting liver dysfunction, advanced liver disease or cirrhosis. Evidence of hepatic impairment that in the opinion of the investigator could interfere with drug metabolism or increase the risk of the known hepatotoxicity of study drug. Any of the following liver function abnormalities: a.Total bilirubin above the upper limit of normal (ULN), excluding patients with Gilbert's syndrome; b.Aspartate or alanine aminotransferase (AST/SGOT or AST/SGPT) > 3 X ULN; c. Alkaline phosphatase > 2.5 X ULN. 13. History of end-stage renal disease requiring dialysis 14. History of unstable or deteriorating cardiac disease, or unstable cardiac arrhythmia or arrhythmia requiring modification of drug therapy, myocardial infarction within the previous year, heart failure requiring hospitalization 15. Any condition that, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone 16. History of alcohol or substance abuse in the past 2 years, at the time of Screening 17. Family or personal history of long QT syndrome 18. Any of the following test criteria above specified limits: a. eGFR < 30 mL/min/1.73m2 b. Electrocardiogram (ECG) with a QTc interval >500 msec at Screening 19. Prior use of pirfenidone or known hypersensitivity to any of the components of study treatment 20. Use of any of the following therapies within 28 days before Screening and during participation in the study: a. Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site b. Potent inhibitors of CYP1A2 (e.g. fluvoxamine, enoxacin), c. Potent inducers of CYP1A2 d. Sildenafil (daily use). Note: intermittent use for erectile dysfunction is allowed 21. Introduction and/or modification of dose of corticosteroids or any cytotoxic, immunosuppressive, or cytokine modulating or receptor antagonist agent for the management of **pulmonary** manifestations of RA, within 3 months of screening, **is** an exclusion criterion, with the exception of dose modification of systemic corticosteroids that

	are maintained at or below 20 mg prednisone daily or the equivalent. However, introduction and/or modification of dose of corticosteroids or any cytotoxic, immunosuppressive, or cytokine modulating or receptor antagonist agent for the management of **extrapulmonary** manifestations of RA **is not** an exclusion criterion for enrollment. 22. Any use of an approved anti-fibrotic medication within 28 days of screening.

SUMMARY SCHEMATIC OF STUDY DESIGN

Visit 1 (week -8 to week 0) SCREENING

- Obtain informed consent
- Screen potential subjects by inclusion and exclusion criteria
- H&P, labs, ECG, HRCT, Spirometry, DL_{CO}, biomarkers (see study assessment calendar for details)

Visit 2 (week 0) ELIGIBILITY/RANDOMIZATION

- H&P, labs, PROs, joint count, Spirometry, biomarkers (see study assessment calendar for details)
- Confirm eligibility and randomize patient
- Treatment Group 1 (n=135)
- Placebo (n=135)
- Dispense study drug
- AE assessment

Visit 3 (week 1) TELEPHONE ASSESSMENT

- Vital status, dosing compliance
- Concomitant medication assessment
- AE assessment

Visit 4 (week 2) TELEPHONE ASSESSMENT

- Vital status, dosing compliance
- Concomitant medication assessment
- AE assessment

Visit 5 (week 4) and Visit 6 (week 8) PROTOCOL VISIT

- H&P, labs, biomarkers (week 4 only), ECG (week 4 only)
- Review drug compliance
- AE assessment

Visit 7 (week 13), Visit 9 (week 26) and Visit 10 (week 39) PROTOCOL VISIT / DISPENSE DRUG

- H&P, labs, biomarkers, PROs, ECG, Spirometry
- Dispense supply of study drug
- AE assessment

Visit 8 (week 19) LAB ASSESSMENT

•Liver function testing
•Concomitant medication assessment
•AE assessment

Visit 11 (week 52) END OF TREATMENT

•H&P, labs, biomarkers, PROs, joint count, Spirometry, DL_{CO}, ECG, HRCT
•Collect diary and unused study drug
•AE assessment

Visit 12 END OF STUDY PHONE CALL (28 DAYS AFTER LAST DOSE OF STUDY DRUG)

- Vital status and AE assessment

PRE-RESTART VISIT

•H&P, labs, ECG
•AE assessment
- Dispense supply of study drug, if required
•Review drug compliance, dispense new diary, if required

UNSCHEDULED VISIT

- H&P, AE assessment
- remaining elements of the visit are up to the discretion of the investigator.

EARLY TERMINATION VISIT

•H&P, labs, biomarkers, PROs, joint count ,Spirometry, DL_{CO}, ECG, HRCT (see study assessment calendar for details)
•Collect diary and unused study drug
•AE assessment

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

2.1.1 RA-ILD

RA is a chronic inflammatory disease that leads to joint damage, deformity, and a high rate of disability and unemployment (Isomaki, Mutru et al. 1975; Allebeck, Ahlbom et al. 1981; Pincus, Callahan et al. 1984; Wolfe, Mitchell et al. 1994; Yelin 1996; Wallberg-Jonsson, Ohman et al. 1997; Gabriel, Crowson et al. 1999; Guedes, Dumont-Fischer et al. 1999). The prevalence of RA is 1-2%, with a 2-fold higher prevalence in women than men (Hochberg and Spector 1990; Doran, Pond et al. 2002). The economic burden of RA is high: direct and indirect costs in the U.S. are estimated at more than 30 billion USD per year, respectively (Lubeck 1994). Furthermore, the lifespan of RA patients is shortened by approximately 10 years (Isomaki, Mutru et al. 1975; Allebeck, Ahlbom et al. 1981; Pincus, Callahan et al. 1984; Wolfe, Mitchell et al. 1994; Yelin 1996; Wallberg-Jonsson, Ohman et al. 1997; Gabriel, Crowson et al. 1999; Guedes, Dumont-Fischer et al. 1999; Doran, Pond et al. 2002), and standardized mortality ratios for RA range from 1.28 to 3.0 (Wolfe, Mitchell et al. 1994).

ILD is a common pulmonary manifestation of RA (Kim 2006). Estimates of the prevalence of ILD vary based on the ascertainment technique: pulmonary function testing (PFT), chest CT or lung biopsy. High-resolution chest CT is more sensitive than PFTs for identifying ILD and is abnormal in 19% of an unselected RA population (Dawson, Fewins et al. 2001) and up to 80% of RA patients with respiratory symptoms (McDonagh, Greaves et al. 1994). The most common radiographic findings on CT are

reticular changes including honeycombing (HC), ground glass opacities (GGO), traction bronchiectasis and consolidation (Cortet, Perez et al. 1997; Dawson, Fewins et al. 2001). Pathologic evaluation on lung biopsy is the most sensitive assessment; ILD was present in 80% of subjects from one case series in which RA patients, not selected for respiratory symptoms, underwent surgical lung biopsies (Cervantes-Perez, Toro-Perez et al. 1980). Among RA patients biopsied for a diagnosis of ILD, usual interstitial pneumonia (UIP) is the most common histopathologic pattern seen (Lamblin, Bergoin et al. 2001), the same pattern seen in patients with idiopathic pulmonary fibrosis. This is in contrast to most other forms of collagen vascular associated-ILD (CVD-ILD), in which non-specific interstitial pneumonitis (NSIP) predominates (Lamblin, Bergoin et al. 2001). This may account, in part, for the poorer prognosis associated with RA-ILD in comparison with other CVD-ILD (Lamblin, Bergoin et al. 2001).

Most patients develop articular symptoms of RA before lung involvement manifests, although these may occur simultaneously (Lee, Kim et al. 2005) or ILD may begin even before articular symptoms are present (Sato, Fujita et al. 2006). The initial symptoms of RA-ILD, when present, are often non-specific, and include dyspnea with exertion and dry cough (Kim 2006). Moreover, the symptoms of RA-ILD overlap with symptoms of other comorbid conditions occurring in RA, such as cardiac disease, and may be missed in early stages due to reduced physical activity masking dyspnea. Interstitial lung disease develops in a progressive fashion presumably following an unrecognized initial insult in a susceptible host. The pathogenesis of the earliest phase of ILD in humans remains unknown. A study which evaluated radiographic progression in a small cohort of RA patients indicated that even in patients with asymptomatic disease, radiographic progression by expert radiologist evaluation (ER) occurs in nearly 60% of patients over an 18 month period (Gochuico, Avila et al. 2008).

Interstitial lung disease (ILD) is a significant contributor to excess mortality in patients with RA. . A long term, population based cohort study of ILD in RA revealed that patients with RA related ILD are at nearly3-fold increased risk of premature death compared to patients without this complication, a risk even higher than that for premature mortality due to cardiovascular disease (Bongartz et al, 2010.) A further longitudinal cohort study showed that RA-ILD is responsible for a significant increase in mortality (Young, Koduri et al. 2007). A recent national study of mortality in RA showed that nearly 10% of the deaths in RA are attributable to ILD (Olson, Swigris et al.) consistent with a prior, single center study (Suzuki, Ohosone et al. 1994). Currently available treatment for RA has achieved a great improvement in the control of articular disease as measured by disease activity and quality of life instruments (van Vollenhoven 2009). Unfortunately, these benefits have not extended to RA-associated lung disease.

2.1.2 Nonclinical Overview Supporting Use in RA-ILD

The mechanism of action of pirfenidone in ILD is thought to be both anti-inflammatory and antifibrotic. Pirfenidone inhibits the synthesis and release of pro-inflammatory cytokines and reduces the accumulation of inflammatory cells in response to various stimuli (Pirfenidone Investigator's Brochure, Edition 11, 2011 and Summary of Product Characteristics, 24 April 2017). Pirfenidone also has been shown to attenuate fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

In rat, hamster, and mouse models of bleomycin-induced lung fibrosis, prophylactic administration of pirfenidone reduced pulmonary fibrosis assessed by both histopathologic analysis and quantitative determination of collagen content. Pirfenidone treatment also reduced pulmonary edema and

pulmonary levels of TGF-β, basic fibroblast growth factor (bFGF), and various pro-inflammatory cytokines.

Thus, both in vitro and in vivo nonclinical studies have provided evidence of reductions in fibroblast proliferation and collagen synthesis, decreased cellular and histologic markers of lung fibrosis, and reduced perturbations in lung function in animal models of fibrosis induction following administration of pirfenidone.

2.1.3 Summary of Findings from Human Clinical Studies

A total of 15 controlled and uncontrolled clinical studies in healthy subjects and patients with IPF or pulmonary fibrosis (PF) have been conducted by Marnac (the original developer of pirfenidone), Shionogi, or InterMune. More than 1300 subjects and patients have received pirfenidone. Other smaller studies of pirfenidone in patients with IPF or PF conducted by independent investigators have been reported in the literature, with generally favorable results (Nagai et al. 2002; Raghu et al. 1999; Gahl et al. 2002). InterMune has conducted multiple Phase 1 studies to assess the clinical pharmacology and safety of pirfenidone as well as two long-term, uncontrolled safety studies that are currently ongoing (PIPF -002 and PIPF -012).

The double-blind, placebo-controlled Phase 2 study conducted by Shionogi in Japan (SP2) served as the initial proof-of-concept study, suggesting a benefit of pirfenidone in patients with IPF. Three Phase 3 studies were subsequently executed independently to confirm these findings, one in Japan (Shionogi-sponsored Phase 3 study [SP3], initiated in July 2004) and two in North America, Europe, and Australia (InterMune-sponsored PIPF-004 and PIPF-006, initiated in July 2006 and April 2006, respectively). Results from SP3, which was ongoing at the start of PIPF-004 and PIPF-006, formed the basis for approval of pirfenidone (Pirespa®) in Japan in October 2008. Efficacy results from these four trials are summarized below.

2.1.3.1 Shionogi Phase 2 Study (SP2) (Azuma et al. 2005)

SP2 was a multicenter, randomized, double-blind, placebo-controlled trial of pirfenidone in patients with a confirmed diagnosis of IPF conducted from 09 November 2000 to 30 September 2002 (Azuma et al. 2005). A total of 109 patients in Japan were randomized in a 2:1 ratio to receive oral pirfenidone (1800 mg/d) or placebo for 52 weeks. Based on a planned interim analysis at 24 weeks, the Efficacy and Safety Assessment Committee recommended stopping the study due to a significantly lower incidence of acute exacerbations, favoring pirfenidone.

In the final analysis at 36 weeks, there was a trend toward a pirfenidone benefit in the primary efficacy outcome variable (mean area-above-the-curve for oxygen saturation by pulse oximetry [SpO2] during the 6-minute steady state exercise test [6MET], 8.12 vs. 8.23; p = 0.093). In secondary analyses, patients receiving pirfenidone had a reduced mean decline from Baseline in vital capacity (VC) (-0.03 L vs. -0.13 L; p = 0.037) and a lower rate of acute exacerbations of IPF (1.4% vs. 14.3%; p = 0.014).

2.1.3.2 Shionogi Phase 3 Study (SP3) (Taniguchi et al. 2010)

SP3 was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study conducted in Japan between 13 July 2004 and 30 August 2006 (Taniguchi et al. 2010). A total of 275 IPF patients from 73 sites were randomized 2:2:1 to receive pirfenidone 1800 mg/d, placebo, or pirfenidone 1200 mg/d for 52 weeks. Sixty-six percent of patients completed the study. SP3 demonstrated a significant benefit of pirfenidone 1800 mg/d compared with placebo on the primary outcome variable of change from Baseline in VC at Week 52 (-90 mL vs. -160 mL; absolute difference 70 mL; relative difference

43.8%; p = 0.042, analysis of covariance [ANCOVA]). There was also a reduced mean decline in %VC at Week 52 in the pirfenidone 1800 mg/d group (-2.91% vs. -5.13%; p = 0.044, ANCOVA).

Progression-free survival (PFS), one of two key pre-specified secondary endpoints, was prolonged in pirfenidone 1800 mg/d-treated patients relative to placebo (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.11–0.79; p = 0.028, log-rank test). In the pirfenidone 1200 mg/d treatment group, there was also a reduced mean decline in VC compared with placebo (-80 mL vs. -160 mL; p = 0.039, ANCOVA), without evidence of a dose response compared with pirfenidone 1800 mg/d.

2.1.3.3 InterMune PIPF-004

In PIPF-004, a multinational, Phase 3, double-blind, placebo-controlled study, 435 patients with IPF were randomized 2:2:1 to receive pirfenidone 2403 mg/d (n = 174), placebo (n = 174), or pirfenidone 1197 mg/d (n = 87). Study treatment lasted from randomization until approximately 72 weeks after the last patient had been randomized in the study. Most patients (84%) completed the study.

In the primary efficacy analysis, treatment with pirfenidone 2403 mg/d resulted in a statistically significant reduction in the mean decline from Baseline in percent predicted forced vital capacity (%FVC) at Week 72 compared with placebo (-8.0% vs. -12.4%; absolute difference 4.4%; relative difference 35.3%; p = 0.001, rank ANCOVA), as well as across all study time points using a repeated measures analysis (p < 0.001). In an analysis of PFS, there was a 36% reduced risk of death or disease progression with pirfenidone 2403 mg/d treatment at Week 72 relative to placebo (HR 0.64; 95% CI 0.44– 0.95; p = 0.023, log-rank test), and a much lower proportion of patients with a decline of ≥10% in %FVC at Week 72 in the pirfenidone 2403 mg/d group (20.1% vs. 34.5%). There was no discernible effect of pirfenidone on other secondary efficacy endpoints.

There was a 39% relative reduction in the risk of death in the pirfenidone 2403 mg/d group compared with placebo (HR 0.61; 95% CI 0.28–1.29; p = 0.191). In the analyses of on-treatment mortality, both the incidence of on-treatment all-cause deaths (i.e., deaths occurring between time of randomization and 28 days after last dose of study treatment and that of IPF-related deaths was lower in the pirfenidone 2403 mg/d group than in the placebo group (10 vs. 14 deaths and 5 vs. 11 deaths, respectively). Evidence of a dose response was observed with pirfenidone 1197 mg/d relative to pirfenidone 2403 mg/d in the analysis of the primary efficacy outcome and several secondary outcome variables.

2.1.3.4 InterMune PIPF-006

PIPF-004 and PIPF-006 studies were identical in almost all major design features; however, PIPF-006 included two rather than three treatment groups. A total of 344 patients were randomized to receive pirfenidone 2403 mg/d (171 patients) or placebo(173 patients). Most patients (83%) completed the study.

The primary efficacy analysis did not reach statistical significance (mean change from Baseline in %FVC at Week 72, -9.0% vs. -9.6%; p = 0.501, rank ANCOVA); however, there was evidence of a treatment effect of pirfenidone 2403 mg/d at multiple earlier time points (p < 0.001 at Week 24, p = 0.011 at Week 36, and p = 0.005 at Week 48). In addition, a repeated measures analysis with averaging across all study time points showed a reduced decline from Baseline in %FVC in pirfenidone 2403 mg/d patients overall (p = 0.007). Also, there was evidence of an effect of pirfenidone 2403 mg/d compared with placebo in the change from Baseline in 6-minute walk test (6MWT) distance at Week 24 (p = 0.038), Week 36 (p = 0.044), Week 48 (p = 0.023), Week 60 (p = 0.014), and Week 72 (p < 0.001, rank ANCOVA). There was no discernable treatment effect of pirfenidone compared with placebo for the

endpoint of PFS (HR 0.84; 95% CI 0.58–1.22; p = 0.355) or in other secondary efficacy endpoints. There was no protective effect on overall survival (HR 0.95; 95% CI 0.48–1.87; p = 0.872). A total of 16 (9.4%) and 17 (9.8%) patients in the pirfenidone 2403 mg/d and placebo groups, respectively, died. However, in the analyses of on-treatment mortality, the incidence of both all-cause deaths and of RA-ILD-related deaths was lower in the pirfenidone 2403 mg/d group than in the placebo group (9 vs. 15 deaths and 7 vs. 14 deaths, respectively).

2.1.3.5 Efficacy Results Across Early Trials

PIPF-004 and PIPF-006

PIPF-004 and PIPF-006 were essentially identical trials by design, and pooling of their data was pre-specified to provide a single, robust estimate of treatment effect. There was a marked reduction in the mean decline from Baseline in %FVC in patients receiving pirfenidone 2403 mg/d compared with placebo at Week 72 (p = 0.005, rank ANCOVA), with the positive treatment effect of pirfenidone beginning at Week 12 (p = 0.003) and sustained throughout every subsequent study time point: Week 24 (p < 0.001), Week 36 (p < 0.001), Week 48 (p < 0.001), and Week 60 (p < 0.001). A repeated-measures analysis of the overall pirfenidone treatment effect on change in %FVC across all study time points also showed a strong benefit compared with placebo (p < 0.001). The proportion of patients with a decrement of ≥10% from Baseline in %FVC at Week 72, a threshold repeatedly found to predict mortality (Collard et al. 2003, Flaherty et al. 2003, King et al. 2005) was 30% lower in patients receiving pirfenidone 2403 mg/d than in patients receiving placebo (21.5% vs. 30.5%).

In addition, treatment with pirfenidone 2403 mg/d resulted in a 26% reduction in the risk of death or progression of disease relative to placebo (HR 0.74; 95% CI 0.57–0.96;p = 0.025), as well as a reduced mean decline from Baseline in 6MWT distance at Week 72 (-52.8 m vs. -76.8 m; absolute difference of 24 m; p < 0.001) and at all earlier study time points after Week 12. Despite the lack of adequate power for the outcome of survival, the risk of death in the pirfenidone 2403 mg/d group relative to placebo was reduced by 23% (HR 0.77; 95% CI 0.47–1.28; p = 0.315), with 7.8% and 9.8% of patients in the two groups dying. In the analyses of on-treatment mortality, the incidence of all-cause death was 35% lower in the pirfenidone 2403 mg/d group than in the placebo group (19 vs. 29 deaths), and the incidence of IPF-related deaths was 52% lower in the pirfenidone 2403 mg/d group than in the placebo group (12 vs. 25 deaths).

PIPF-004, PIPF-006, SP3, and SP2

Standardized estimates of the magnitude of the treatment effect on FVC/VC were derived from PIPF-004, PIPF-006, SP3, and SP2 to facilitate a direct comparison of study results (Figure 1-1). PIPF-004 and PIPF-006 analyzed change from Baseline in %FVC at time points that included Weeks 24, 36, 48, and 72, whereas SP3 and SP2 assessed the change from Baseline in VC at time points that included Weeks 28 and 36. SP3 also included an assessment at Week 52. The results show a high level of consistency in these results across time points (with the exception of Week 72) and across these studies. In addition, all of the meta-analysis estimates favor pirfenidone and clearly exclude no effect. At the Week 48/52 time point, point estimates of effect are remarkably similar in the three Phase 3 studies, and the confidence intervals in all 3 studies exclude the null effect.

A similar consistency in the hazard ratios for PFS was found for the 3 studies that included this endpoint (i.e., PIPF-004, PIPF-006, and SP3): a recent independent meta- analysis by the Cochrane Review (Spagnolo 2010) of these three Phase 3 trials (N = 1046) demonstrated significant improvement in PFS, with an overall 30% reduction in the risk of death or disease progression (HR 0.70; 95% CI 0.56, 0.88; p = 0.002).

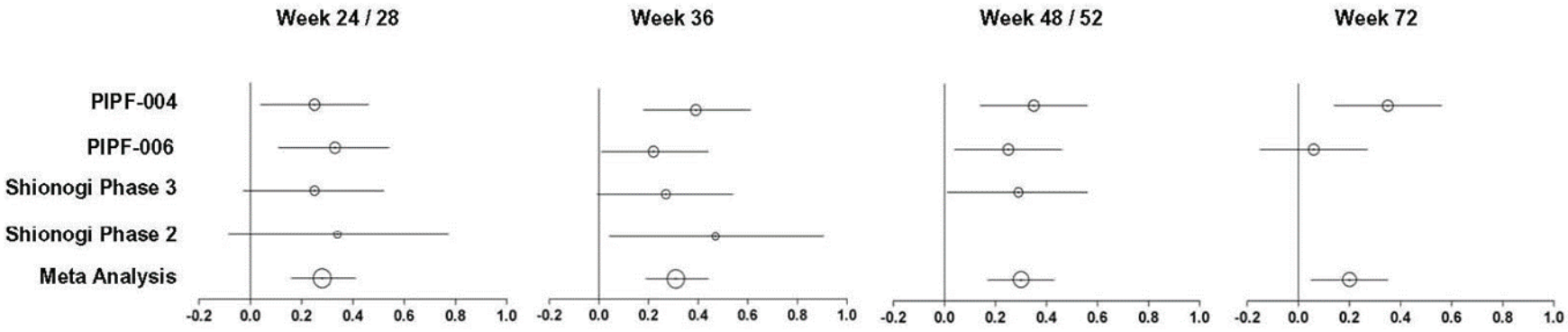


Figure 1 . Individual Study and Meta-analysis Estimates of the Pirfenidone Treatment Effect on VC/FVC Across Time Points

Line represents standardized treatment effect of pirfenidone vs. placebo and 95% confidence interval. The dose of pirfenidone was 2403 mg/d in PIPF-004 and PIPF-006 and was 1800 mg/d in SP3 and SP2.

2.1.3.6 InterMune Pooled Phase 3 Safety Data

Safety results from the pooled PIPF-004 and PIPF-006 pirfenidone 2403 mg/d study population were similar to those in previous studies. Common treatment-emergent adverse events (AE) that occurred more frequently in the pirfenidone group than the placebo group included gastrointestinal disorders (nausea, diarrhea, dyspepsia, vomiting, and stomach discomfort), skin disorders (rash and photosensitivity reaction), anorexia, decreased appetite, fatigue, and dizziness. Although more pirfenidone 2403 mg/d than placebo patients had at least 1 dose reduction for at least 1 day, dose reductions implemented in accordance with the protocol-specified guidelines tended to be short-lived and were typically related to transient gastrointestinal events or skin disorders. The rate of treatment discontinuation due to an AE in the pirfenidone 2403 mg/d group was only 6% higher than in the placebo group. Mild or moderate serum transaminase elevations (serum ALT or AST >3 × upper limit of normal [ULN]) occurred more frequently in patients treated with pirfenidone 2403 mg/d than placebo, but they were most often effectively managed with dose modification and not associated with untoward clinical consequences. More extreme elevations in serum ALT or AST (>10 × ULN) were rare in both treatment groups, and no instances of liver function abnormality meeting the criteria for Hy's law occurred.

Intermune ASCEND Trial

In the ASCEND Trial, a multinational, Phase 3, double blind, placebo-controlled study, 555 patients with IPF were randomized to receive pirfenidone 2403 mg/d (n=278) or placebo (n=277). Study treatment lasted from randomization until approximately 52 weeks after the last patient had been randomized in the study. Most patients (94.1%) completed the study.

In the primary efficacy analysis, treatment with pirfenidone 2403 mg/d resulted in a statistically significant reduction in the mean decline from Baseline in percent predicted forced vital capacity (%FVC) at Week 52 compared with placebo (235ml vs. 428ml; absolute difference 193ml; relative difference 45.1%; p <0.001, rank ANCOVA). At week 52, the proportion of patients who had a decline in FVC% by 10 percentage points or had died was reduced by 47.9% in the pirfenidone group (16.5% vs. 31.8%).

In the secondary efficacy analysis, pirfendone resulted in a significant between group difference in the 6-minute walk distance (25.9% in the pirfenidone group and 35.7% in the placebo group had a decrease in 6-minute walk distance of 50m or more at week 52, P=0.04) and the combined endpoint of reduction in risk of death or disease progression (reduced by 43% in the pirfenidone group, HR 0.57, 95% CI 0.43 to 0.77, P<0.001). There were no differences in dyspnea as measures by the UCSD SOBQ scores at week 52 or all cause mortality. In a pooled analysis of all-cause mortality (555 patients from ASCEND and 692 from CAPACITY), there was a reduction in the risk of death at 1 year by 48% (HR 0.52, 95% CI 0.31 to 0.87, P=0.01).

2.2 RATIONALE AND STUDY APPROACH

RA-ILD is a life-threatening and severely debilitating disease characterized by poor survival and a lack of efficacious therapeutic options at the inception of this study. Results from four controlled trials, as described above, suggest that pirfenidone treatment is safe and well tolerated in IPF with efficacy in a variety of domains, including changes in lung volume (%FVC/VC) and 6MWD over time, exercise tolerance (change in 6MWT distance), progression-free survival time, and all-cause mortality. Thus,

pirfenidone may be of benefit in RA-ILD, which shares many histopathological and clinic-epidemiological features with IPF (including poor survival).

Given the loss of lung volumes over time in patients with RA-ILD, this protocol is designed to evaluate whether pirfenidone 2403 mg/d reduces decline in FVC or mortality over 52 weeks, compared with placebo, in patients with RA-ILD.

This is a multi-center, randomized, double blind, placebo-controlled trial to assess the safety and tolerability of pirfenidone 2403 mg/day for the treatment of RA-associated interstitial lung disease.

The protocol eligibility criteria include a probable/definite diagnosis of RA and associated lung disease. These criteria must be met in patients with % predicted FVC ≥40% and % predicted DL_{CO} ≥25% PFT criteria which overlap closely with eligibility criteria in prior studies demonstrating the efficacy of pirfenidone for the treatment of IPF. FVC and DL_{CO} criteria have been minimally liberalized to optimize enrollment in the more limited population of patients with autoimmune ILD.

The primary composite endpoint of progression-free survival represents a clinically meaningful outcome measure that has been demonstrated to be reliable, valid, and predictive of changes in other disease states (King, Bradford et al. 2014). Exploratory endpoints include a number of, clinical, serologic and biomarker endpoints with the potential to serve as markers of response to therapy.

Multiple previous authors have reported that a decrement in % FVC over 6 months, particularly if ≥ 10% in magnitude, is both clinically significant and highly predictive of mortality (Collard et al. 2003; Flaherty et al. 2003; Zappala et al. 2010). We have chosen to assess the change in % FVC over the more prolonged duration of 12 months (52 weeks), which is twice the 6-month duration used in many of the studies assessing the performance characteristics of FVC. Decrements in % FVC at 12 months have also been robustly associated with mortality (Collard et al. 2003; {Latsi, 2003 #4006} King et al. 2005).

Investigators propose to to test the validity and responsiveness to change of patient reported outcomes in the TRAIL-1 study. Composite indices have revolutionized the drug development in rheumatology due to multisystem involvement of these disorders. Given the heterogeneity of rheumatic diseases, outcome measures show high variability across individual patients, and may even vary with time with the same patient. The premise of a composite index is that it will capture divergent aspects of the disease, including patient-reported outcomes, that are important to the patient and clinician, while reducing variability associated with each individual outcome measure. A composite measure is more sensitive to change because its precision is better than that of individual components. This precision can be achieved by combining measure that have modest correlation. Well-validated, widely accepted combined response indices are more likely to be responsive to change than individual measures, which translates into greater power to detect differences; facilitate drug development; and improve assessment of efficacy of therapeutic agents.

Pirfenidone 2403 mg/d was the dose evaluated in studies of pirfenidone in IPF, which demonstrated favorable efficacy and safety results compared with placebo.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 Known Potential Risks

The safety of pirfenidone has been characterized in 16 studies involving 1900 subjects and patients; 1055 patients have received pirfenidone at a dose of 2403 mg/d or greater. Analyses of these data suggest that the side effects of pirfenidone are readily monitored, typically reversible, and related to tolerability rather than morbidity. Drug-induced liver injury (DILI) in the form of transient and clinically silent elevations in transaminases, has been commonly reported and in rare cases, these elevations were associated with concomitant bilirubin increases. Non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported In the post marketing period. Escalation of dose over the first 2 weeks, dosing with food, use of protection against sun exposure, prompt symptomatic management of intolerance, and monitoring of liver function tests during dosing are recommended to maximize tolerability.

2.3.2 Known Potential Benefits

The collective data from InterMune-sponsored PIPF-004 and PIPF-006, as well as Shionogi sponsored SP3 and SP2 and the ASCEND Trial, provide evidence that pirfenidone provides a clinically meaningful benefit to patients with IPF as measured by lung function, exercise tolerance, and progression-free survival.

3 STUDY OBJECTIVES AND PURPOSE

The objectives of this study of pirfenidone in patients with RA-ILD are as follows:

1. To assess the efficacy and safety of pirfenidone 2403 mg/day as compared to placebo in patients with RA-associated interstitial lung disease.

2. To explore the role of peripheral blood biomarkers in predicting disease progression and survival in patients with RA-associated interstitial lung disease.

3. To explore a spectrum of validated questionnaires to assess disease specific PROs including overall health, and perspectives on symptoms, performance and quality of life.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a phase 2, randomized, double blind, placebo controlled trial of pirfenidone for the treatment of RA associated interstitial lung disease. Approximately 270 subjects will be randomized to receive pirfenidone 2403 mg per day or placebo in a 1:1 ratio. The primary aim of this study is to assess the efficacy and safety of pirfenidone 2403 mg/day versus placebo in patients with RA-associated interstitial lung disease. The primary efficacy outcome is defined by a composite endpoint of decline from baseline in percent predicted FVC of 10% or greater or death during the 52-week treatment period. Patients will receive blinded study treatment from the time of randomization until the Week 52 Visit.

Eligible patients aged 18 to 85 years must meet 2010 ACR/EULAR criteria for RA (Aletaha, Neogi et al. 2010) as well as RA-associated ILD, as determined by imaging and, when available, lung biopsy. Patients will be required to have a percent predicted FVC ≥40% and percent predicted DL_{CO} ≥25% at screening. Any patient identified for the study must discontinue all prohibited therapies for at least 28 days before the start of screening. The Screening Period may last up to 56 days.

The dose of study treatment will be titrated over 14 days. Patients will receive a telephone assessment at Weeks 1 and 2, and visit the clinic at Weeks 4, 8, 13, 19, 26, 39, and 52. Patients should complete a treatment compliance diary between visits. If patients discontinue study treatment for any reason before the end of the study, they should complete an unscheduled visit and continue with all scheduled study procedures through Week 52. If subjects are unable to complete the study visits as scheduled, all efforts should be made to complete an early termination visit. All subjects will receive an end of study phone call 28 days post last dose of study drug to assess vital status and adverse events.

4.2 STUDY ENDPOINTS

4.2.1 Primary Endpoint

The primary outcome variable of this study will be the incidence of the composite endpoint of decline from baseline in percent predicted FVC of 10% or greater or death during the study treatment period.

4.2.2 Secondary Endpoints

Secondary outcome measures of efficacy for this study will be assessed from baseline to the 52-week treatment period and will include:

1. Incidence of the composite endpoint of decline from baseline in percent predicted FVC of 10% or greater during the study period.
2. Frequency of progressive disease as defined by OMERACT:

   Relative decline from baseline in percent predicted FVC of ≥10%, or relative decline from baseline in percent predicted FVC ≥ 5% and < 10%, and ≥15% relative decline in $DL_{CO\ predicted}$ (Khanna, Mittoo et al. 2015)
3. Change from baseline to end of study in absolute value of FVC
4. Change from baseline to end of study of percent predicted FVC
5. Slope of percent predicted FVC over study period
6. Slope of absolute FVC over study period
7. Time to decline of 10% or greater in percent predicted FVC or death over study period
8. Proportion of participants with all-cause mortality
9. Proportion of participants with all-cause hospitalization
10. Proportion of participants with hospitalization for respiratory cause
11. Number of respiratory exacerbations requiring hospitalizations

12. Proportion of participants with and number of treatment-emergent AEs
13. Proportion of participants with and number of treatment-emergent serious adverse events (SAEs)
14. Proportion of participants with and number of treatment-emergent/treatment-related AEs
15. Proportion of participants with and number of treatment-emergent/treatment-related SAEs
16. Proportion of participants with and number of AEs leading to early discontinuation of study treatment
17. Proportion of participants with and number of treatment-emergent death or transplant
18. Proportion of participants with and number of treatment-emergent RA-ILD-related mortality
19. Change from Baseline to end of study in dyspnea, as measured by the Dyspnea 12 questionnaire

4.2.3 Exploratory Endpoints

Exploratory endpoints will include the following:

1. Change from Baseline to end of study for Disease Activity Score (DAS)
2. Change from Baseline to end of study for RAPID3 score (RA disease activity score)
3. Change from Baseline to end of study in Erythrocyte Sedimentation Rate (ESR)
4. Change from Baseline to end of study in C-Reactive Protein (CRP)
5. Candidate biomarker expression in the peripheral blood of patients with RA-ILD over the study period of treatment and the study follow-up period
6. Changes from Baseline to end of study in HRCT parameters evaluated by quantitative functional imaging
7. Changes from Baseline to Week 13, 26, 39 and 52 in the St. George's Respiratory Questionnaire (SGRQ)
8. Changes from Baseline to Week 13, 26, 39 and 52 in Dyspnea 12 questionnaire
9. Changes from Baseline to Week 13, 26, 39 and 52 in Leicester Cough Questionnaire (LCQ)
10. Changes from Baseline to Week 13, 26, 39 and 52 in the Patient global assessment
11. Changes from Baseline to Week 13, 26, 39 and 52 in the Health assessment questionnaire

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this study.

Patients must fulfill all of the following criteria to be eligible for enrollment in the study:

1. Age 18 through 85 years, inclusive, at Screening

2. Probable or definite diagnosis of RA according to revised 2010 ACR/EULAR criteria, without evidence or suspicion of an alternative diagnosis that may contribute to their interstitial lung disease.
3. Diagnosis of ILD
    a. supported by clinically indicated HRCT, and when available, surgical lung biopsy (SLB), prior to Screening, and
    b. presence of fibrotic abnormality affecting more than 10% of the lung parenchyma, with or without traction bronchiectasis or honeycombing, on Screening and confirmed by adjudicated HRCT prior to Baseline
4. No features supporting an alternative diagnosis on transbronchial biopsy, or SLB, if performed prior to Screening
5. Attainment of the following centralized spirometry criteria (based on local spirometry on standardized equipment and centralized quality controlled):
    a. percent predicted FVC ≥ 40% at Screening
    b. change in pre-bronchodilator FVC (measured in liters) between Visit 1 (Screening) and Visit 2 (Randomization) must be a <10% relative difference, calculated as:
    100% * [absolute value (Visit 1 FVC – Visit 2 FVC) / Visit 1 FVC]
    c. percent predicted DL_{CO} or TL_{CO} ≥25 % at Screening
    d. Screening (Visit 1) pre-bronchodilator(BD) and Post-BD spirometry meets ATS quality criteria as determined by a central reviewer
    e. Baseline (Visit 2) Pre-BD spirometry meets ATS quality criteria as determined by the site Investigator or the central reviewer

6. Able to understand and sign a written informed consent form.
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of <1% per year, during the 52 week treatment period and for at least 118 days after the last dose of study drug.
    a. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    b. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
8. For men who are not surgically sterile: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
    a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of

< 1% per year during the treatment period and for at least 118 days after the last dose of study drug.

b. Men must refrain from donating sperm during this same period.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Not a suitable candidate for enrollment or unlikely to comply with the requirements of this study, in the opinion of the investigator
2. Cigarette smoking or vaping within 3 months of Screening or unwilling to avoid tobacco products throughout the study
3. History of clinically significant environmental exposure known to cause pulmonary fibrosis (PF), including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds
4. Concurrent presence of the following conditions:
   a. Other interstitial lung disease, related to but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, or bronchiolitis obliterans organizing pneumonia
   b. Medical history including Human Immunodeficiency Virus (HIV)
   c. Medical history of viral hepatitis (positive Hep A antibody in the absence of elevated liver enzymes is not an exclusion)
5. Concurrent presence of other pleuropulmonary manifestations of RA, including but not limited to rheumatoid nodular disease of the lung, pleuritis/pleural thickening, and obliterative bronchiolitis
6. Post-bronchodilator FEV1/FVC <0.65 at Screening
7. Presence of pleural effusion occupying more than 20% of the hemithorax on Screening HRCT
8. Clinical diagnosis of a second connective tissue disease or overlap syndrome (including but not limited to scleroderma, sjogren's, polymyositis/dermatomyositis, systemic lupus erythematosus but excluding Raynaud's phenomena)
9. Coexistent clinically significant COPD/emphysema or asthma in the opinion of the site principal investigator
10. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis. The infection should be resolved per PI assessment prior to enrollment. Any use of antibiotics must be completed 2weeks prior to the screening visit. Note that prophylactic antibiotics are not contraindicated or exclusionary
11. Any history of malignancy diagnosed within 5 years of screening, other than basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or low grade cervical carcinoma, and/or low grade prostate cancer.
    Criteria for low grade prostate cancer:
    - Patients with suspicion for prostate cancer based on PSA and/or DRE should have been evaluated by urology
    - Patients with NCCN very low risk prostate cancer (· T1c and Grade Group 1 (Gleason 6) and PSA <10 ng/mL and Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/coreg and · PSA density <0.15 ng/mL/g) can be monitored without intervention and enrolled in study.
    - Patients with NCCN low risk prostate cancer can be monitored on a case by case basis (T1-T2a and Grade Group 1 (Gleason 6) and · PSA <10 ng/mL) and enrolled in study.
    - All other patients should be excluded.

12. History of LFT abnormalities as outlined below, or imaging, laboratory or other clinical information suggesting liver dysfunction, advanced liver disease or cirrhosis. Evidence of hepatic impairment that in the opinion of the investigator could interfere with drug metabolism or increase the risk of the known hepatotoxicity of study drug.

    Any of the following liver function abnormalities:
    a. Total bilirubin above the upper limit of normal (ULN), excluding patients with Gilbert's syndrome;
    b. Aspartate or alanine aminotransferase (AST/SGOT or AST/SGPT) > 3 X ULN;
    c. Alkaline phosphatase > 2.5 X ULN.

13. History of end-stage renal disease requiring dialysis

14. History of unstable or deteriorating cardiac disease, or unstable cardiac arrhythmia or arrhythmia requiring modification of drug therapy, myocardial infarction within the previous year, heart failure requiring hospitalization.

15. Any condition that, in the opinion of the investigator, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone

16. History of alcohol or substance abuse in the past 2 years, at the time of Screening

17. Family or personal history of long QT syndrome

18. Any of the following test criteria above specified limits:

    a. Estimated glomerular filtration rate <30 mL/min/1.73m2
    b. ECG with a QTc interval >500 msec at Screening

19. Prior use of pirfenidone or known hypersensitivity to any of the components of study treatment

20. Use of any of the following therapies within 28 days before Screening and during participation in the study:

    a. Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site
    b. Potent inhibitors of CYP1A2(e.g. fluvoxamine, enoxacin)
    c. Potent inducers of CYP1A2.
    d. Sildenafil (daily use). Note: intermittent use for erectile dysfunction is allowed

21. Introduction and/or modification of dose of corticosteroids or any cytotoxic, immunosuppressive, or cytokine modulating or receptor antagonist agent for the management of **pulmonary** manifestations of RA, within 3 months of screening, **is** an exclusion criterion for enrollment, with the exception of dose modification of systemic corticosteroids that are maintained at or below 20 mg prednisone daily or the equivalent.

However, introduction and/or modification of dose of corticosteroids or any cytotoxic, immunosuppressive, or cytokine modulating or receptor antagonist agent for the management of **extrapulmonary** manifestations of RA **is not** an exclusion criterion for enrollment.

22. Any use of an approved anti-fibrotic medication within 28 days of screening.

5.3 PARTICIPANT WITHDRAWAL OR TERMINATION

5.3.1 Reasons for Withdrawal or Termination

Study treatment will be discontinued for any of the following reasons:

- Unacceptable toxicity (this may include serious adverse events [SAEs] related to study treatment)
- Participant request or withdrawal of consent
- Pregnancy
- Investigator discretion
- Termination of study by Genentech
- Lung transplantation

5.3.2 Handling of Participant Withdrawals or Termination

It is critical to the integrity of this study that participants adhere to the visit schedule outlined in the protocol. As such, every reasonable effort should be made to convey the importance of remaining on study to the participants. Any participant discontinuing study drug (Section 5.3.3) or terminating participation in the study (Section 5.3.4) must be reported immediately by telephone to the medical monitor or designee to discuss the circumstances of the case in an effort to ensure participant safety and appropriate documentation of events.

5.3.3 Early Discontinuation of Study Drug

Participants who discontinue study treatment before Week 52 will complete an Unscheduled Visit related to discontinuation of study drug and potential safety issues, as necessary. If such a visit would occur within +/- one week of a regularly scheduled visit at week 4-,8-,13-,26-, or 39- then the regularly scheduled study visit can replace an unscheduled visit, otherwise the subject should be brought in for an unscheduled visit. Whenever possible, they will continue to complete all scheduled study assessments and procedures through Week 52. Participants who permanently discontinue study drug before Week 52 must return unused study drug.

5.3.4 Early Termination Visit

Participants who withdraw consent in writing will cease all study procedures including vital status assessments. These participants will complete an Early Termination Visit (Section 7.2.2) and Visit 12/End of Study Phone Call 28 days after the last dose of study drug, whenever possible.

Participants may have clinically appropriate testing in preparation for lung transplantation while on

the study. Participants who receive a lung transplant during the study will discontinue study treatment and withdraw from study procedures. These participants will also complete an Early Termination Visit (Section 7.2.2) and Visit 12/End of Study Phone Call 28 days after the last dose of study drug, whenever possible.

5.3.5 Study Treatment Pre-Restart Visits

Participants should be encouraged to restart study treatment whenever possible and appropriate. If the participant has interrupted study treatment for ≥28 days, a Pre-Restart Visit is required (Section 7.2.2). The Pre-Restart Visit will be conducted on the day study treatment is resumed.
Participants who restart study treatment will resume the visit schedule based on their date of randomization. If a regularly scheduled visit (Weeks 13, 26, 39, etc.) coincides with the Pre-Restart Visit, then all of the elements of the regularly scheduled visit should be performed in lieu of the Pre-Restart Visit.

5.3.6 Unscheduled Visits

Any follow-up that is performed to monitor participant safety should be collected as an Unscheduled Visit (Section 7.2.2). The investigator is responsible for review of AEs/SAEs, concomitant medications, oxygen use, physical examination, resting oxygen saturation, vital signs, and weight. The remaining elements of the visit are up to the discretion of the investigator. Any additional clinical laboratory assessments should be obtained through the central laboratory.

5.3.7 Lost to Follow-Up

If a participant has missed a visit and is not responding to telephone calls from the site (all attempts to contact the participant should be documented), the site will need to take more aggressive action in locating the participant. The site should make at least two attempts to contact the participant by telephone and two additional attempts to contact the participant's emergency contact. If these attempts are not successful, a registered letter should be sent to the last known address of the participant. If after all of these methods are employed and no contact with the participant results, the participant will be considered lost to follow-up. In this circumstance, the site should check the national death registries, where approved by regulatory authorities and available, to obtain vital status information for the database.

5.4 PREMATURE TERMINATION OR SUSPENSION OF STUDY

Both the Sponsor or designee and the Investigator reserve the right to terminate the study at the Investigator's site, according to the terms of the study contract. The Investigator/Sponsor or designee should notify the IEC/IRB and relevant national competent authorities in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

The Sponsor or designee reserves the right to terminate the study overall.

5.5 APPROVAL OF NINTEDANIB (OFEV) IN THE UNITED STATES

On March 9, 2020 the U.S. Food and Drug Administration approved OFEV (nintedanib) oral capsules for the treatment of chronic fibrosing (scarring) interstitial lung disease (ILD), such as RA-ILD. All US participants currently enrolled in the study were contacted to inform them of this new information and affirm their desire to continue participating in the study or not. Neither OFEV nor Pirfendone have been approved for use in patient with RA-ILD in Australia, Canada, or the United Kingdom.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 Source and Acquisition of Study Drugs

Genentech will supply all study medications (pirfenidone and matching placebo). There will be 270 capsules per bottle, which will be labeled for investigational use only. Pirfenidone 267-mg and placebo will be supplied in opaque, hard, white gelatin capsules that are visually indistinguishable.

6.1.2 Study Agent Formulation, Appearance, Packaging and Labeling

The contents of the pirfenidone 267-mg capsules are as follows:

- Pirfenidone 82.15%
- Croscarmellose sodium 8.15%
- Microcrystalline cellulose 7.39%
- Povidone, USP, EP 1.85%
- Magnesium stearate 0.46%

The contents of the placebo capsules are as follows:

- Microcrystalline cellulose 79.99%
- Pre-gel starch 19.5%
- Magnesium stearate 0.5%
- Bitrex 0.01%

6.1.3 Product Storage & Stability

Study medication will be shipped to the investigational sites at ambient temperature and should be stored between 15 and 30° C. DO NOT FREEZE OR REFRIGERATE. Do not use beyond the expiration date.

6.1.4 Dispensing of Study Treatment

Study treatment will be dispensed to the participant every 13 weeks, but may be dispensed at other visits, as needed. Participants will be instructed to store study treatment at room temperature. Participants will be instructed to use study treatments in the order in which they are dispensed and that they must return all used and unused study treatment bottles.

6.1.5 Pre-specified Dose Adjustment & Modifications

It is the responsibility of the investigator to monitor participants as frequently as clinically indicated for toxicities and consistent with the instructions of the package inserts for any medication used to treat study participants. Refer to Section 2.1 for safety data from Genentech's Phase 3 clinical studies of pirfenidone.

If a participant experiences significant side effects, treatment of symptoms and/or temporary dose reductions, interruptions, or discontinuation of study treatment should be considered. Investigators have experience of using Pirfenidone with IPF patients, however, a suggested dosing flowchart is attached at Appendix B. Any such dosing modifications should be recorded in the participant diary. The medical monitor or designee will be available to discuss the management of AEs and dose modification, as needed.

In the event of elevated liver aminotransferase tests, the recommendations in Table 1 should be followed. The medical monitor or designee may be contacted for further discussion, as needed.

Table 1. Recommended Procedures for Participants with Elevated Liver Aminotransferase Test Results

Magnitude of Elevation in ALT or AST	Recommendation
>3 to ≤5 × ULN **Not accompanied** by symptoms or hyperbilirubinemia (Total bilirubin >2 × ULN)	Exclude other causes (e.g. confounding medications). Monitor the patient closely, including repeat liver chemistry tests. If clinically appropriate, reduce or interrupt the dose (e.g., until liver chemistry test results are within normal limits). Once liver function tests are again within normal limits, Esbriet may be re-titrated to the recommended daily dose if tolerated. Liver function tests should be repeated at 1 month intervals until < 3 x ULN
>3 to ≤5 × ULN **Accompanied** by hyperbilirubinemia (Total bilirubin >2 × ULN) *or clinical signs or symptoms of liver injury** **Refer to section 6.1.19 for clinical signs of symptoms*	Study treatment should be permanently discontinued. Liver function tests should be monitored monthly until symptoms resolve and bilirubin < 2 x ULN
>5 × ULN	Study treatment should be permanently discontinued. Liver function tests should be monitored monthly until < 3 x ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

In the event of a QTc >500 msec, refer to Section 7.1.2 for instructions.

With the exceptions noted above, study treatment may be restarted at the discretion of the investigator. For treatment interruptions of ≥28 days, a pre-restart visit is required, as outlined in Section 6.1.8, in addition to study treatment titration.

Investigators should use the flowchart in Appedix B to re-titrate subjects to full dose. However if the subject is unable to tolerate the full dose, the subject will be maintained on the highest dose tolerable for the remainder of the study. Dosing changes and interruptions will be recorded.

In participants requiring hospitalization for an acute pulmonary process of unclear etiology, the investigator should consider continuing study treatment, if appropriate. If the participant is hospitalized at an institution other than the study site, the treating physician should be encouraged

to discuss the participant's management with the investigator at the earliest possible time. All records pertaining to the hospitalization should be obtained.

All toxicities will be followed according to procedures in Section 8.The ultimate decision regarding study treatment interruption, restart, and dose modification is the responsibility of the investigator. For example, it is the investigator's responsibility to determine whether study treatment should be restarted in the setting of changing toxicity grades. Investigators are encouraged to contact the medical monitor or designee to discuss participant safety and dose-modification issues.

6.1.6 Duration of Therapy

Study treatment is defined as either pirfenidone 2403 mg/d or placebo equivalent administered in divided doses three times per day (TID). Each dose should be taken with food, at the same time each day, preferably after each meal.

Dose Escalation Period: Study treatment should be titrated over 14 days, as tolerated, to the full dose of 9 capsules per day (three capsules TID), as follows:

- Days 1–7: one capsule TID
- Days 8–14: two capsules TID
- Days 15-21: three capsules TID (maximum of 9 capsules daily)

Stable Dosing Period: Participants will remain on a stable maintenance dose for the duration of the study period (Day 22 to Week 52) unless the dose is reduced to manage an AE (see Section 6.1.5).

Doses of more than 9 capsules per day are not recommended for any participant.

6.1.7 Missed Doses

If participants miss a scheduled dose, that dose should be skipped. Regular dosing should resume with the next scheduled dose. Participants should not take any extra doses to make up for missed doses.

6.1.8 Interruption of Study Treatment

Any participant with an actual or anticipated interruption of study treatment for a period of ≥28 consecutive days will be reported by telephone to the study's medical monitor or designee to discuss the circumstances of the case. Once the participant restarts study treatment, the dose may be re-titrated as described in Section 6.1.6. A pre-restart visit is required, as described in Section 5.3.5.

6.1.9 Precautionary Measures

Drug-induced liver injury (DILI) has been observed with pirfenidone. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with pirfenidone had a higher incidence of ALT and/or AST elevations of ≥3x ULN (3.7%) compared with placebo patients (0.8%). Increases in ALT and AST ≥3x ULN were reversible with dose modification or treatment discontinuation.

Measure liver function promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations. See Table 1.

Pirfenidone is causally associated with DILI, mainly in the form of transient liver enzyme elevations of no clinical relevance. However, clinical manifestations of DILI including cases with fatal outcome – possibly caused by idiosyncratic reactions to pirfenidone – have been reported in rare instances.

Exposure to sunlight (including sunlamps and tanning beds) should be avoided or minimized during study treatment due to the possibility of photosensitivity reactions or rash. Participants should be instructed to use sunscreens that have a sun protection factor (SPF) of 50 or higher as well as protection against ultraviolet A (UV-A) radiation, and also to wear clothing that protects against sun exposure and avoid concomitant medications known to cause photosensitivity reactions, if possible.

All doses of study treatment are to be taken with food to reduce the likelihood of gastrointestinal symptoms. The dose titration period of 21 days at the initiation of study treatment is designed to maximize tolerability.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The monitoring of the inventory of study treatment supplies may be delegated to the responsible pharmacist; however, the Investigator is ultimately responsible for monitoring of study treatment inventory. Study treatment may not be used for any purpose other than that described in the protocol. All study treatment must be stored in a secure place with access restricted to authorized personnel.

Participants should return all used and unused bottles of study treatment at every visit. After drug accountability has been assessed and drug return has been authorized by the clinical monitor, sites may return all used and unused study treatment bottles to the distribution center or destroyed in accordance with site-specific standard operating procedures.

All bottles of study treatment will be recorded in a Drug Accountability Log. The Investigator or designee will account for all study treatment received at the site, dispensed to the participants, returned by the participants, not used, and destroyed. All documentation of study treatment shipments must be retained.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

Informed consent must be obtained prior to Screening and before any study-mandated procedures take place. Study procedures are defined as laboratory tests, spirometry, lung volumes, DL_{CO} (carbon monoxide transfer capacity), ECG, HRCT scan, directed history, physical examination, vital signs, height, weight, and any changes to existing treatment regimens. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in Appendix A. If any study procedure related to PFTs and imaging is deemed not acceptable for quality issues, the procedure should be repeated.

7.1.1 Laboratory Assessments

Routine Clinical Laboratory Tests

The following research related assessments will be performed locally at each clinical site, according to Appendix A, as summarized below:

- Hematology (complete blood count with platelet count and automated differential)
- Serum chemistry profile (albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, calcium, creatinine, glomerular filtration rate (eGRF), gamma-glutamyl transferase [GGT], glucose, potassium, sodium, BUN, uric acid and amylase)
- Blood Pregnancy test for women of childbearing capacity
- Serology assessments include Erythrocyte Sedimentation Rate (ESR), Rheumatoid Factor (RF), C-Reactive Protein (CRP), and Cyclic Citrullinated Peptide (CCP)

It is the investigator's responsibility to perform clinical laboratory assessments more frequently, if clinically indicated.

Biomarkers in Blood

Research laboratory studies will be conducted at Baylor College of Medicine. Blood samples obtained for research studies will be shipped to Baylor College of Medicine. Biomarker samples include Serum, Plasma, and RNA. These samples will be collected according to Appendix A. Samples will be labeled with a unique study code and stored at the Biorepository at Baylor College of Medicine for future research.

Certain biomarkers may be differentially expressed in RA-ILD and may change as a result of pirfenidone treatment (e.g., possibly cytokines, chemokines, microRNA expression, and other cellular and molecular markers of fibrosis). The blood samples that are being obtained for this study may help identify these biomarkers and may be used to assess their response to pirfenidone therapy.

Genetic Polymorphisms (Assessed at Participating Sites)

Genetic polymorphisms have been demonstrated to alter the development and clinical course of a number of different diseases. The purpose of assessing genetic polymorphisms in this study is to understand their potential role in the pathogenesis of RA-ILD and in clinical outcomes.

The assessment of genetic polymorphisms will be conducted at all institutions that agree to offer this assessment. Participant participation for this assessment is voluntary and declining participation will in no way influence eligibility for this study. Participants agreeing to participate will opt in on the informed consent form. Blood samples for genetic research include DNA PAXgene samples. These samples will be collected according to Appendix A. Samples will be labeled with a unique study code and stored at the Biorepository at Baylor College of Medicine for future research.

7.1.2 Clinical Assessments

HRCT Scans

HRCT scans obtained before the Screening period as part of the standard of care for a participant may be used to confirm eligibility, provided they meet all of the image acquisition and quality criteria required by the central expert readers and were obtained within 3 months before the start of the Screening Period (see Appendix A). All HRCT digital images are to be stored on a dedicated disk or tape at each study center. The images will be transferred electronically to the vendor tasked with interpretation and archiving of the images.

To assess for eligibility, HRCT scans will be evaluated for:

a. presence and extent (to nearest 10%) of reticular abnormality, ground glass, honeycombing, mosaic attenuation, nodules, consolidation, emphysema, overall extent of fibrosis.

b. Semi-quantitative estimates of extent by central reader.

c. Presence of traction bronchiectasis, non-traction bronchiectasis (common in RA), subpleural sparing, centrilobular nodularity, tree in bud, crazy paving, pleural thickening and/or effusion.

d. Distribution of abnormalities:

   i. Subpleural, peribronchovascular predominance or diffuse in axial plane

   ii. Upper lung, mid lung, lower lung predominance or diffuse in craniocaudal plane

e. Radiologic pattern of abnormality: UIP, NSIP, indeterminate, mixed (Lynch DA, Godwin JD, Safrin S, Starko KM, Hormel P, Brown KK, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005 Aug 15;172(4):488-93.)

The HRCT scans will be reviewed by a central reader who is a radiologist with expertise in RA-ILD prior to randomization. An adjudication committee will be available to assist with difficult cases. Data regarding the HRCT interpretation will be entered electronically into the Data Coordinating Center (DCC) database and incorporated into the clinical database.

Surgical lung biopsy

Surgical lung biopsy (SLB) or transbronchial biopsy, if performed, may be obtained up to 4 years before randomization. Data regarding the pathology findings will be entered directly into the electronic case report form (eCRF). Participant eligibility will be communicated to the study site by the investigators' designated vendor.

Spirometry and DL_{CO}/ TL_{CO} Measurements

All equipment, procedures, and personnel qualifications for the assessment of lung function are based on the recommendations of the American Thoracic Society (ATS 2005) and will be performed and interpreted in accordance with published guidelines (Crapo 1994):

Spirometry measurements will include FVC and FEV_1 before and 10-15 minutes after administration of a bronchodilator [albuterol (or salbutamol) from a metered dose inhaler] at screening. The remainder of the spirometric studies will be performed without bronchodilator administration.

Lung volume measurements will be performed by body plethysmography and should be performed before or at least 30 min after the last bronchodilator puff.

DL_{CO}/ TL_{CO} will be measured by determining the diffusing capacity of the lung for carbon monoxide.

DL_{CO}/ TL_{CO} measurement should be performed before or at least 30 min after the last bronchodilator puff.

All FVC data collected throughout the study will be evaluated by a central reader blinded to treatment assignment. Data for FVC and FEV_1, will be entered electronically into the vendor's database and incorporated into the clinical database. DL_{CO}/ TL_{CO} will be entered into the clinical database by the site.

Patient Reported Outcomes

A spectrum of validated questionnaires will be used to assessed patient related outcomes that include disease specific, overall health, and their perspectives on symptoms, performance and quality of life. These questionnaires have been endorsed by the OMERACT as the essential core set that should be included in the trials of Connective Tissue Disease-Interstitial Lung Disease. Domains that are advocated include: 1. Health Related Quality of Life (HRQOL), 2. Dyspnea, 3. Cough, 4. Patient Global Assessment, and 5. Function.

a) HRQOL instrument: St. George's Respiratory Questionnaire (SGRQ): SGRQ, a respiratory disease-specific HRQOL instrument that was originally developed for use in chronic obstructive pulmonary disease, has more recently been used in interstitial lung disease.

b) Dyspnea: Dyspnea 12 questionnaire (D-12): The D-12 is a unidimensional questionnaire with 12 items that provides a global score of breathlessness severity that incorporates both "physical" and "affective" aspects. The score is calculated using simple summation of the responses for each item (0 "mild" to 3 "severe"); thus, the total score ranges from 0 to 36, with 36 representing maximal severity. It has been validated in Connective Tissue Disease-Interstitial Lung Disease.

c) Cough: Leicester Cough Questionnaire (LCQ): This self-administered 19-item questionnaire for the quantitative assessment of symptoms of cough frequency and severity.

d) Patient global assessment (DAS28 Section B Global Health Questionnaire): DAS28 Section B Is a single item visual analog scale that assesses global severity of the patient due to their disease.

e) Function: Health assessment questionnaire (HAQ20): It is a 20-item questionnaire to assess daily functional disability. It is validated in RA and is universally used in clinical trials of RA.

f) RAPID3: The Routine Assessment of Patient Index Data 3 (RAPID3) is a questionnaire that has been validated for rheumatoid arthritis to assess patient physical function, pain, and global assessment.

Physical Exam and Vital Signs

A complete physical examination should be performed on the day of the visit, including all body systems pertinent to the participant. If clinically significant abnormalities are observed before Day 1, they should be reported in the participant's medical history. If clinically significant abnormalities are observed after Day 1, the investigator should decide if they are new adverse events. Vital signs for this study protocol include heart rate and blood pressure.

Disease Activity Score (DAS28)

The DAS28 will be scored by an investigator based on clinical examination including swollen and tender joint counts performed by the investigators and lab results (ESR and CRP), as well as patient global assessment score.

Physician Global Assessment

Physician Global Assessment questionnaire asks physicians to rate the patient's overall health in the last week.

Vital Status Assessments

Vital status must be assessed at protocol-specified time points until the Follow-Up Visit, even if the participant cannot physically be present for the visit. Participants who chose to withdraw from study procedures early will be followed for vital status until Visit 12/End of Study Phone Call whenever possible.
Vital status procedures are as follows:

1. In the case of lung transplant, the date of the transplant, details of the transplant, dates of hospitalization, and the current vital status will be obtained
2. In the case of participant death, the date, details, and cause of death will be obtained if possible
3. If a participant is lost to follow-up, vital status will be ascertained through the use of Death Registries, where approved and available (see 5.3.7)

Mortality Assessment Committee

A Mortality Assessment Committee (MAC) will closely examine the details and review the relationship to RA-ILD for each death. Documentation regarding deaths must be requested and should include (but is not limited to) discharge summaries, death certificates, and autopsy reports.

Adjudication of Acute Exacerbations

An adjudication committee will be established to assess whether episodes of respiratory decompensation/acute exacerbation are congruent with established criteria, and their relationships to study treatment.

Electrocardiograms (ECGs)

ECGs should be performed before bronchodilator administration or on a separate day.

During the study, if the QTc interval is >550 msec, confirmed by a repeat ECG within 24 h, and verified by the study site or local cardiologist, study drug should be stopped. If the QTc interval is between 500 and 550 msec, confirmed by a repeat ECG within 24 hours, and verified by a study site or local cardiologist, study treatment should be interrupted. If an alternative explanation is identified (e.g., electrolyte abnormality or concomitant medication), re-initiation of study treatment may be considered by the investigator in consultation with the medical monitor or designee. ECG data will be incorporated into the clinical database.

7.2 SUMMARY OF STUDY SCHEDULE AND ASSESSMENTS

7.2.1 Screening Period

Written informed consent must be obtained before initiating any study-associated procedures or changes to a pre-existing treatment regimen for purposes of this study. Procedures conducted during screening will be used to determine the eligibility of each participant for study inclusion before randomization and to establish participant baseline status.

Subjects who do not meet enrollment criteria at Visit 1 may be brought back to be rescreened for potential enrollment. Each subject may only complete up to one rescreening visit. The rationale to rescreen includes factors that may be subject to change over time such as a condition that subsequently resolves (e.g. infection), change in concomitant medication (e.g. dose of corticosteroids is stabilized or a prohibited medication has been completed/discontinued), change in smoking history (e.g. smoking history now greater than within 3 months of screening), spirometry criteria, or lab assessment criteria. In such cases, all Visit 1 procedures will be repeated. HRCT scans performed within 3 months of the start date of the screening period may be used to confirm eligibility.

Screening (Visit 1)

The Screening period (Visit 1) is defined as the time between the date of the first Screening procedure and Eligibility/Randomization (Visit 2) and may last up to 56 days. Screening procedures may be conducted on different days within the Screening period if convenient.

The following procedures will be performed during Screening:

1. Written informed consent

2. Directed medical history/review of systems, review of AEs/SAEs, concomitant medications, oxygen use

3. Physical examination, vital signs, resting oxygen saturation, weight, and height

4. Clinical laboratory assessments, including hematology, serum chemistries, serologic tests, and blood pregnancy test for women of childbearing capacity

5. ECG (obtained before bronchodilator administration or on a separate day)

6. Measurement of Oxygen Saturation at Rest

7 . Review of transbronchial biopsy or SLB, if available, to assess eligibility

8. HRCT scan to assess eligibility

9 . Spirometry (FVC, FEV_1) before and 10-15 minutes after bronchodilator administration

10. Lung volumes, DL_{CO} or TL_{CO} obtained before or 30 minutes after bronchodilator administration

11. Biomarkers (See Appendix A)

Eligibility and Randomization (Visit 2)

All Visit 2 procedures must be performed before randomization and before administration of study treatment. Randomization (Visit 2) will occur no more than 56 days after the start of the Screening period, and study treatment should begin on the day of randomization. All results of the screening assessments and eligibility documentation will be submitted to study investigators or designee for approval *at least 2 working days* before the targeted randomization day. Once a participant's documentation is received and the participant is confirmed to be eligible for randomization, the site will be instructed to randomize the participant at the end of Visit 2.

The following procedures will be performed at Visit 2:

Before Randomization:

1. Directed medical history/review of systems,review of AEs/SAEs, concomitant medications, oxygen use

2. Physical examination, resting oxygen saturation, vital signs, and weight

3. Pregnancy test for women of childbearing capacity

4. Biomarkers (See Appendix A)

5. Blood samples for genetic research (DNA PAXgene samples) - Optional

6. Spirometry (FVC, FEV_1) without bronchodilator administration

7. Patient Reported Outcome Questionnaires (See Appendix A)

8. Disease Activity Score (DAS28): Swollen and Tender Joint Counts and patient global assessment score

9. Confirmation of participant eligibility for study participation

Randomization:

10. Randomize participant using an automated system

After Randomization:

11. Instruct the participant on how to titrate the dose of study treatment

12. Dispense supply of study treatment. On day of randomization, first dose must be taken in clinic and Study Medication Accountability completed.

13. Dispense participant diary and instruct participants on how to properly record information using the diary

7.2.2 Assessments During Treatment

Weeks 1 and 2 (Visit 3, 4) (± 2 days) Telephone Assessment

A telephone interview will be conducted for Vital Status Assessment, review of AEs/SAEs, concomitant medications, and study medication dosing.

Weeks 4 and 8 (Visit 5, 6) (± 1 week)

The following procedures will be performed at Weeks 4 and 8:

1. Review of AEs/SAEs, concomitant medications, oxygen use
2. Physical examination, resting oxygen saturation, vital signs, and weight
3. ECG (at Week 4 only)
4. Clinical laboratory assessments, including hematology, serum chemistries, and blood pregnancy test for women of childbearing capacity
5. Study Medication Dosing review (participant diary)
6. Biomarkers (Week 4 only)

Weeks 13, 26, 39 (Visit 7, 9, 10) (± 2 weeks)

The following will be performed at Weeks 13, 26, and 39:

1. Review of AEs/SAEs, concomitant medications, oxygen use
2. Physical examination, resting oxygen saturation, vital signs, and weight
3. ECG
4. Spirometry (FVC, FEV_1) without bronchodilator administration

5. Clinical laboratory assessments, including hematology, serum chemistries, blood pregnancy test for women of childbearing capacity
6. Biomarkers
7. Patient Reported Outcome Questionnaires (See Appendix A)
8. Study Medication Accountability, including dispensing of study treatment
9. Study Medication Dosing review (participant diary)
10. Dispense new diary, if required.

Week 19 (Visit 8) (± 1 week)

The following will be performed at Week 19:

1. Review of AEs/SAEs, concomitant medications
2. Liver function testing only (AST, ALT, bilirubin, and alkaline phosphatase)

Week 52 (Visit 11) (± 4 weeks)

At the Week 52 Visit, the following procedures will be performed:

1. Review of AEs/SAEs, concomitant medications, oxygen use
2. Physical examination, resting oxygen saturation, vital signs, and weight
3. Clinical laboratory assessments, including hematology, serum chemistries, serologic tests, and blood pregnancy test for women of childbearing capacity
4. Biomarkers (See Appendix A)
5. Blood samples for genetic research (DNA PAXgene samples) - Optional
6. Spirometry (FVC, FEV1 without bronchodilator administration)
7. Lung volumes, DL_{CO} or TL_{CO}
8. Patient Reported Outcome Questionnaires (See Appendix A)
9. Study Medication Accountability, including collection of any unused study treatment
10. Study Medication Dosing review (participant diary)
11. HRCT scan
12. ECG

13. Disease Activity Score (DAS28): Swollen and Tender Joint Counts and patient global assessment score

Visit 12/End of Study Phone Call (28 days after last dose of study drug, ± 1 week)

1. Review of AEs/SAEs
2. Vital Status Assessment

Early Termination Visit

Participants who terminate participation in the study (e.g. withdraw consent in writing, receive a lung transplant) will discontinue study treatment, cease all study procedures, and undergo the assessments listed below. These participants will also complete Visit 12/End of Study Phone Call 28 days after the last dose of study drug.

1. Review of AEs/SAEs, concomitant medications, oxygen use
2. Physical examination, resting oxygen saturation, vital signs, and weight
3. Clinical laboratory assessments, including hematology, serum chemistries, serologic tests, and blood pregnancy test for women of childbearing capacity
4. Biomarkers (See Appendix A)
5. Blood samples for genetic research (DNA PAXgene samples) - Optional
6. Spirometry (FVC, FEV1 without bronchodilator administration)
7. Lung volumes, DLCO or TLCO
8. Patient Reported Outcome Questionnaires (See Appendix A)
9. Study Medication Accountability, including collection of any unused study treatment
10. Study Medication Dosing review (participant diary)
11. HRCT scan
12. ECG
13. Disease Activity Score (DAS28): Swollen and Tender Joint Counts and patient global assessment score

Study Treatment Pre-Restart Visits

If the participant has interrupted study treatment for ≥28 days, a Pre-Restart Visit is required. The following procedures will be performed at the Pre-Restart Visit:

1. Review of AEs/SAEs, concomitant medications, oxygen use

2. Physical examination, resting oxygen saturation, vital signs, and weight
3. Clinical laboratory assessments, including hematology, serum chemistries, and blood pregnancy test for women of childbearing capacity
4. ECG
5. Study Medication Accountability, including dispensing of study treatment, if required
6. Study Medication Dosing review (participant diary)
7. Instruction on how to re-titrate the dose of study treatment
8. Dispense new diary, if required

Unscheduled Visits

The following procedures are required to be performed at Unscheduled Visits to monitor participant safety:

1. Review of AEs/SAEs, concomitant medications, oxygen use
2. Physical examination, resting oxygen saturation, vital signs, and weight
3. Study Medication Accountability
4. Study Medication Dosing review (participant diary)

Further evaluation as part of routine clinical care would be done at the discretion of the site Principal Investigator.

Participants who discontinue study drug early will complete an Unscheduled Visit. These participants will then continue to complete all scheduled study assessments and procedures through Week 52 (Visit 11).

7.3 CONCOMITANT MEDICATIONS & TREATMENTS DURING THE STUDY

7.3.1 Concomitant Medications

All of the following are considered concomitant medications, and data regarding their use must be collected and recorded:

- Prescription drugs
- Over-the-counter drugs, including vitamins, antacids, herbal and dietary supplements
- Permitted therapies (see section 5.1)
- Excluded therapies (see Section 7.4)

Information on all concomitant medications will be collected until 28 days after the last dose of study treatment.

7.3.2 Treatment for Acute ILD Exacerbations

Acute ILD exacerbations should be identified in accordance with published guidelines.(Raghu, Collard et al. 2011) Corticosteroids may be used at the discretion of the investigator, without dose restriction, for a period of up to 21 days in participants experiencing an episode of acute ILD exacerbation. The study drug should be continued during this time, if possible. If study treatment interruption/discontinuation is being considered, it must be immediately reported by telephone to the medical monitor or designee to discuss the circumstances of the case.

7.4 PROHIBITED MEDICATIONS AND TREATMENTS DURING THE STUDY

Pirfenidone is metabolised by Cytochrome P450 1A2 (CYP1A2). Inhibitors of this enzyme will increase drug levels and inducers reduce them. Potent inhibitors and activators should be avoided. Use of medications with moderate and mild activator and inhibitor effects on study drug metabolism is left to the discretion of the site PI.

The following medications are not permitted on this study - strong inhbitors of CYP1A2 including but not limited to Fluvoxamine and Enoxacin.

The following moderate inhibitors of CYP1A2 medications should be used with caution: Amiodarone, Propafenone, Ciprofloxacin. Pirfenidone should be reduced to 1602 mg daily (2 capsules, 3 times a day) if taken with Ciprofloxacin 750mg twice daily. Special care should also be exercised if CYP1A2 inhibitors are being used concomitantly with potent inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone such as CYP2C9 (e.g. amiodarone, fluconazole), 2C19 (e.g. chloramphenicol) and 2D6 (e.g. fluoxetine, paroxetine).

Moderate inducers of CYP1A2 may reduce the effective dose of pirfenidone and should be used with caution.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Investigators are responsible for monitoring the safety of participants who have entered this study and for providing appropriate medical care. In addition, the investigators are responsible for alerting Genentech and/or Roche or its designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the participant. A SAE should be reported to the medical monitor or designee within 24 hours after becoming aware of its occurrence via reporting in the study database. Investigators must report all SAEs to their governing IRB/IEC as required by local regulations and guidelines.

By exercising appropriate health-care options, the investigator remains responsible for managing AEs that are serious or that cause the participants to withdraw before completing the study. Duration of follow-up and requirements for immediate SAE reporting (within 24 hours of the event) are described below.

8.2 SAFETY DATA EXCHANGE AGREEMENT

8.2.1 Background

The relevant International Conference on Harmonization (ICH) guidelines, the latest European Union Pharmacovigilance guidelines and applicable European Union legislation, the United States (US) Code of Federal Regulations, Title 21, and relevant local regulations form the basis of the information to be exchanged under this protocol and to be reported to the regulatory authorities, as applicable.

8.2.2 Definitions

Single Case Management

- Collection of Single Case Reports
  - The PI or his designee (i.e., the DCC) will collect all protocol-defined Adverse Events (AEs) and pregnancy reports from the Study and obtain follow-up information on incomplete AE and pregnancy reports.
- Tracking of Safety Information
  - The PI or his designee (i.e., the DCC) will track all protocol-defined AE and pregnancy reports originating from the Study for the Product. The PI will also track all Serious Adverse Drug Reactions (SADRs) associated with other Investigational Medicinal Products (IMPs), (i.e., excluding the Product), as defined in the protocol.

Exchange of Single Case Reports

Serious Adverse Events (SAEs), pregnancy reports, where the participant has been exposed to the Product, will be sent on a MedWatch or CIOMS I form to the Roche contact via the DCC. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- SADRs
  Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Roche via the Data Coordinating Center (DCC) within fifteen (15) calendar days of the awareness date.

- Other SAEs
  Serious AE reports that are unrelated to the Product shall be transmitted to Roche via the DCC within thirty (30) calendar days of the awareness date.

- Pregnancy reports
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Roche via the DCC within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

[Note: For all reports, an acceptable format includes MedWatch or CIOMS I form, or Roche approved reporting forms. If the Sponsor is unable to use these formats then line-listings can be used as detailed in the Global: Investigator Initiated Study Safety Data Exchange Management (WI-0100195).]

Case Transmission Verification of Single Case Reports

The investigators will ensure that all single case reports have been adequately received by Roche, via a periodic line-listing documenting single case reports sent by the PI to Roche by the DCC via email in the preceding time period (e.g., monthly).

Confirmation of receipt should be received within the time period mutually agreed upon.

Following Case Transmission Verification, single case reports which have not been received by Roche shall be forwarded by the investigators (via the DCC) to Roche within five (5) calendar days from request by Roche.

8.2.3 Randomization Codes for Blinded Clinical Trials

The blind will be broken for ADR reports that are serious and unexpected, unless otherwise agreed with applicable regulatory authorities.

8.2.4 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The PI will be responsible for the expedited reporting of safety reports originating from the Study to the regulatory authorities in those countries where it has filed a clinical trial approval, in compliance with local regulations.

The PI will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM).The PI will be responsible for expedited reporting of safety reports originating from the Study to the Ethics Committees of the concerned Member States, where applicable.

The PI will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

The PI will be responsible for the preparation of six-monthly SUSAR reports and their submission to investigators, regulatory authorities and Ethics Committees, where applicable.

Aggregate Reports

- Development Safety Update Report

The PI will be responsible for the preparation of a Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The PI will provide the DSUR to Roche as soon as reasonably possible after completion.

Roche will forward to the PI an executive summary of the Roche DSUR upon request. The PI may cross-reference the executive summary of the Roche DSUR, as applicable.

- Other Reports

The PI will forward quarterly listings of non-serious AEs originating from the Study to Roche.

Queries

Queries related to the Study will be answered by the PI. However, responses to all safety queries from regulatory authorities or for publications will be discussed with Roche. Roche shall have the final say and control over safety queries relating to the Product. The PI will not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Roche.

All reasonable effort will be made to ensure that deadlines for responses to urgent requests for information or review of data are met.

Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the PI will contact Roche as soon as possible.

8.2.5 Language

English will be used as the common language for all safety information exchanged between the Parties.

8.2.6 Records

The PI will maintain reports and all related documentation (or true copies of these documents) for a time period required by the applicable laws and regulations in the territories for which they are responsible, taking into account the minimum archiving period worldwide.

8.3 AE AND SAE SEVERITY GRADES AND RELATIONSHIP TO STUDY TREATMENT

The seriousness of an AE should not be confused with its severity. The severity of AEs is to be graded according to the following guidelines:

Grade 1–Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/ therapy required

Grade 2–Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required

Grade 3–Severe: Marked limitation in activity; some assistance usually required; medical intervention or therapy required, hospitalization possible

Grade 4–Life Threatening: Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5-Death

The relationship of study treatment to the AE will be determined by the investigator based on the following definitions:

Not Related: Another cause of the event is most plausible; and/or clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; and/or a causal relationship is considered biologically implausible.

Possibly Related: An event that follows a reasonable temporal sequence from administration of the study treatment, or follows a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.

Probably Related: An event that follows a reasonable temporal sequence from administration of the study treatment, and there is a biologically plausible mechanism for study treatment causing or contributing to the AE and the event could not be reasonably explained by the known characteristics of the patient's clinical state. In addition, the relationship may be confirmed by improvement of the event on stopping study treatment and reappearance of the event on repeated exposure to study treatment.

8.3.1 Adverse Event Reporting

All AEs will be graded for severity and relevance to study agents as detailed above, and recorded with start dates occurring any time after informed consent is obtained until at least 7 (for non-serious AEs or 28 days for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. A record of all AEs, by study subject, will be recorded centrally by the DCC.

8.3.2 Serious Adverse Event Reporting

All SAEs will be graded for severity and relevance to study agents as detailed above, and recorded with start dates occurring any time after informed consent is obtained until 28 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of SAEs since the last visit and study participants and their significant others will be asked in advance to

notify the study investigators immediately regarding any hospitalization, serious change in their health or in the event of a death. Events will be followed for outcome information until resolution or stabilization.

Regardless of whether the SAE is deemed related to use of the study agents, the data for the SAE must be reported with the appropriate information by the study investigators or their designee within 24 hours of learning of the event. In addition, new follow-up data must be reported within 24 hours of receipt. The medical monitor or designee may be contacted at any time for immediate discussion regarding such an event.

Investigators must report all SAEs to their governing IRB/IEC, as required by local regulations and guidelines.

Deaths in patients who withdraw from study procedures early and continue with Vital Status Assessments will not be considered SAEs if the death occurs more than 28 days after last dose of study treatment.

A record of all SAEs, by study subject, will be databased by the DCC.

8.3.3 Unexpected Adverse Event Reporting

All adverse events that meet the definition of an unanticipated problem should be reported to the local governing IRB within specific timelines as described below: The Unanticipated Problem (UP) report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.3.3.1 **Reporting to the IRB required within 10 working days:**

- Any internal or external adverse event (unanticipated problem) which meets all of the following criteria:
  a) Unexpected (in occurance, severity or in frequency of occurance that was not previously known and/or described in the approved informed consent document or other protocol related documents),
  b) and Related or possibly related to the research participation,
  c) and places subjects or others at greater risk of harm than was previously known or recognized (i.e. a serious adverse event, a new or increased risk to subjects/others)

8.3.3.2 **Reporting within 3 working days:**

- An SAE, including subject death, that meet all of the following criteria:
  a) Occurred in an interventional study (i.e., involving a drug, biologic, device procedure and/or behavioral interventions),
  b) Unexpected,
  c) and judged to be related or possibly related to research participation

8.3.4 Reporting of Pregnancy

Pregnancies should be reported from the time the patient signs the informed consent form until the final study visit. Study treatment must be immediately discontinued if a patient becomes pregnant. Although pregnancy is not considered an SAE, all pregnancies should be reported as SAEs to the study sponsors. Pregnancies must be followed until termination of pregnancy or for a minimum of 6 months after the birth of the child.

8.4 SAFETY OVERSIGHT

Safety oversight will be under the direction of an external Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise in RA-ILD, the study drugs and/or clinical trials research including experts in Rheumatology, Pulmonary Medicine, Internal Medicine and/or Bioethics, and Biostatistics. The DSMB Chair will be appointed by the Study Executive Committee from among experts in the field who are not otherwise actively involved in the conduct of the Clinical Study or its reporting or analysis and who do not have an active appointment with any of the participating institutions. The DSMB Chair will then independently select the remainder of the Committee Members using similar expertise and affiliation criteria.

Once the trial is initiated, the DSMB will review cumulative trial results to evaluate the treatment for adverse effects, including the review of all AEs, SAEs and UP. The board will also monitor the performance of individual clinics and study performance indicators (drug monitoring and compliance, visit compliance, recruitment, etc.). The DSMB will meet approximiately every 6 months by teleconference and/or web videoconferencing for the duration of the trial and will interact directly with the DCC for access to study data and interim reports.

The DSMB will be charged to provide external oversight concerning the safety and scientific integrity of the study for the duration of the clinical trial. Written reports will be produced that will advise study sites as to whether the study is approved to continue as is, specific safety and/or data management procedures will need to be addressed/implemented for ongoing approval, or whether the study should be stopped due to specific safety or ethical management concerns.

The DCC will provide the DSMB with all of the study related information that it requires to carry out its directive.

9 CLINICAL MONITORING

Throughout the course of the study, data will be monitored for accuracy and completeness and study procedures will be monitored for adherence to the protocol and Good Clinical Practices (GCP). In addition to frequent contacts through e-mail and telephone, on-site monitoring visits will be coordinated by the Statistical Analysis of Biomedical and Educational Research (SABER) unit at the University of Michigan. SABER (the Data Coordinating Center for this study) will be responsible for operational aspects and monitoring of the trial, including at least annual monitoring visits and/or remote source data verification.

The clinical monitor will ensure that:

- Data collected and entered into the database are verifiable against source documents for the participants. The clinical monitor will need access to subject medical records and other study-related records needed to verify the entries on the electronic case report forms.

- Appropriate consent is obtained for each participant prior to study procedures.
- The rights and well-being of participants are being protected.
- The study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol), with any other study agreements, with GCP and with applicable regulatory requirements.
- Study medication is properly dispensed and accounted for. The study monitor will also perform drug accountability checks and review the clinical site's regulatory document binder to assure completeness of documentation in all respects of clinical study conduct.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10 STATISTICAL CONSIDERATIONS

The objectives of the study are to assess the efficacy and safety of pirfenidone2403 mg/d compared with placebo in the treatment of participants with RA-ILD. A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. The SAP will be finalized prior to unblinding of the data.

Baseline is defined as values from assessments and testing done during the Sceening period.

10.1 RANDOMIZATION AND TREATMENT ASSIGNMENT

Eligible participants will be screened and once determined to be eligible, informed consent will be obtained. Participants will then be randomized with equal probability to receive either Pirfenidone or placebo in a double-blinded fashion. Treatment assignments will not be re-used; each consecutive randomized participant will receive the next consecutive unused treatment assignment. The password protected computer text file that contains the translation of treatment labels A and B to either Pirfenidone or placebo will be maintained by the unblinded DCC statistician.

10.2 SAMPLE SIZE AND POWER CONSIDERATIONS

10.2.1 Primary endpoint:

Table 1A shows sample size calculations and Table 1B shows power that will be achieved for some feasible scenarios with the selected sample size. Hypothesized estimates of treatment response in both placebo and pirfenidone arms were derived from the report of the Pirfenidone trial in IPF (King, et al., 2014.) If participants with RA-ILD are similar, then the proposed sample size of 254 participants (127 per group) will provide 85% power to demonstrate the treatment difference in terms of the combined primary endpoint reached by week 52, defined as either death or a decline from baseline of $\geq$10 percentage points in the percent predicted FVC. It is possible that participants with RA-ILD will have fewer endpoints than participants with IPF. Table 1B and Figure 1 show that power will remain sufficient for several scenarios where participants have fewer endpoints, and showing the robustness of the power to slight deviations from the hypothesized treatment estimates with the selected sample size. The **number of participants randomized will be 270** because of possible loss of data due to participants dropping out before week 52 or other reasons.

PASS version 13 was used for power calculations (PASS 13 Power Analysis and Sample Size Software, 2014, NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

Table 1: Power analysis for combined major endpoint reached by week 52, defined as either death or a decline from baseline of ≥10 percentage points in the percent predicted FVC.

A. Sample Size Calculation, 5% alpha, 2-sided

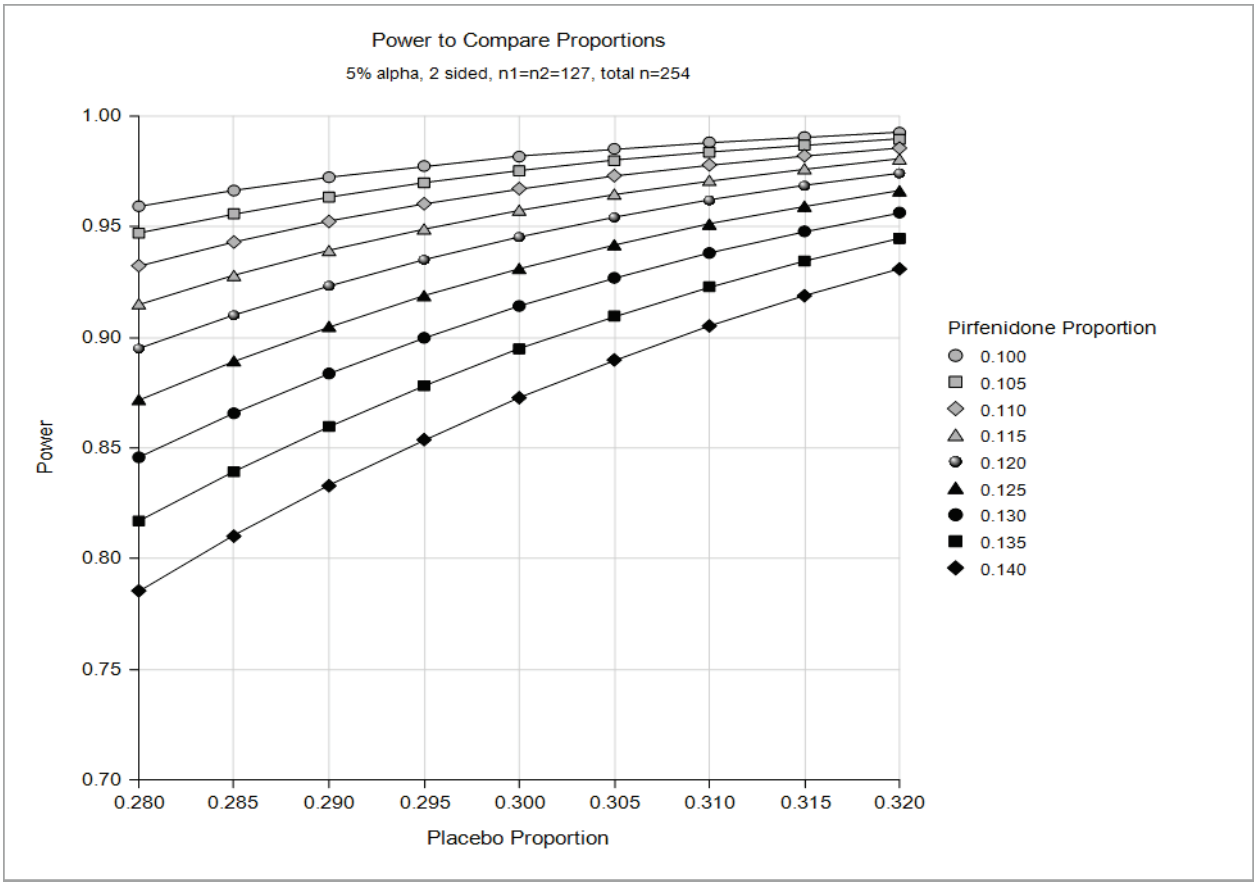
Power	Sample Size Each Arm	Total Sample Size	Proportion Placebo	Proportion Pirfenidone	Difference
0.80	141	282	0.30	0.16	0.14
0.85	161	322	0.30	0.16	0.14
0.90	188	376	0.30	0.16	0.14
0.80	111	222	0.32	0.16	0.16
0.85	**127**	**254***	**0.32**	**0.16**	**0.16**
0.90	148	296	0.32	0.16	0.16

* The anticipated total number of participants is 254.

B. Possible Scenarios with fewer endpoints, 127 on each arm (254 total), 5% alpha, 2 sided.

Proportion Placebo	Proportion Pirfenidone	Difference	Power
0.24	0.08	0.16	0.94
0.24	0.10	0.14	0.85
0.24	0.11	0.13	0.78
0.26	0.08	0.18	0.97
0.26	0.10	0.16	0.92
0.26	0.12	0.14	0.82
0.28	0.12	0.16	0.89
0.28	0.13	0.15	0.85
0.28	0.14	0.14	0.79
0.29	0.13	0.16	0.88
0.29	0.14	0.15	0.83
0.29	0.15	0.14	0.77
0.30	0.14	0.16	0.87
0.30	0.15	0.15	0.82
0.30	0.16	0.14	0.76
0.31	0.15	0.16	0.86
0.31	0.16	0.15	0.81
0.32	0.15	0.17	0.90
0.32	0.16	0.16	0.85

Figure 1:



10.2.2 Secondary and exploratory endpoints:

All analyses of secondary outcomes will be exploratory. Observed effect sizes will be useful to inform the design of future confirmatory trials and provide supportive information about consistency or lack thereof of pirfenidone on clinical outcomes. Additional exploratory analyses will incorporate data from Quantitative Imaging Analysis of Parenchymal Lung Abnormalities, data from Biomarker Analysis, and Patient Reported Assessments as described in the assessments and study objective sections above.

10.3 ADVERSE EVENTS

Table 2A shows the probability of observing at least one adverse event among participants randomized to Pirfenidone under a range of assumptions for the background adverse event rate. The proposed sample size of 127 participants randomized to Pirfenidone will provide a 72% probability of observing an adverse event with a 1% background rate and a 99% probability of observing an adverse event that has a 3.5% background rate. Furthermore, with a goal of estimating an adverse event rate for this population with sufficient precision based on the proposed sample size, Table 2B shows that the two-sided 95%

confidence interval around the observed proportion will be sufficiently narrow for a range of adverse event rates.

Table 2A: Probability of observing at least one adverse event in the pirfenidone group (N=127), under a range of background adverse event rates.

Background Adverse Event Rate	Probability of Observing at Least One Adverse Event
0.010	0.72
0.020	0.92
0.035	0.99
0.050	1.00
0.100	1.00
0.150	1.00
0.200	1.00

Table 2B: Two-sided 95% confidence interval width for a range of observed adverse event proportions with 127 participants on Pirfenidone with complete data.

Observed Proportion	Confidence Interval Width	Lower Limit	Upper Limit
0.025	0.064	0.006	0.069
0.050	0.084	0.019	0.104
0.075	0.100	0.036	0.135
0.100	0.112	0.054	0.166
0.125	0.122	0.073	0.195
0.150	0.131	0.093	0.224
0.175	0.139	0.113	0.252
0.200	0.146	0.134	0.280

10.4 STATISTICAL ANALYSIS

10.4.1 Analysis Populations

The intention to treat (ITT) population will include all participants randomized and will be used to assess primary, secondary and exploratory efficacy outcomes. The as-treated population will include all randomized participants who received at least one dose of study medication and will be used to assess safety outcomes. An additional secondary analysis dataset will be used to assess the robustness of the primary efficacy endpoint: The per protocol dataset is defined as the ITT population excluding patients who are noncompliant with study medication and who have major protocol deviations.

10.4.2 Efficacy Analyses

Demographic data and baseline characteristics will be summarized by treatment arm. The primary analysis population will be the ITT population. The main analysis framework will be logistic regression to assess treatment differences in the primary outcome, defined as either death or a decline from baseline of $\geq$10 percentage points in percent predicted FVC, reached by week 52. Baseline for spirometry is defined as the screening visit with the assumption that values are the same at randomization. Baseline for other variables is defined as the randomization visit for variables collected at randomization, otherwise as the screening visit. The main predictor will be treatment arm, and covariates known to be related to the outcome and specified a priori (i.e., prior to database lock and unblinding), will be considered for inclusion. The stratification factor will be the site. Unadjusted and adjusted odds ratios, 95% confidence intervals and Wald test p-values will be reported. Similar analyses will be conducted with the listed secondary binary outcomes in Section 4.2.2. An additional secondary analysis of the primary endpoint will use the Per Protocol population.

Statistical analyses of the secondary outcomes that describe time-to-event will use Cox proportional hazards regressions using a similar approach as described above, reporting adjusted hazard ratios, 95% confidence intervals and p-values. Time will be measured from randomization until the event or until censoring. Kaplan-Meier plots will be generated, and proportionality of hazards will be assessed.

There are a number of secondary and exploratory outcome variables that are continuous, that will be calculated for each subject as follows: Each change from baseline to week 52 outcome will be calculated as the last value minus the baseline value. Each slope outcome will be derived from a linear regression of the values over the treatment period. The molecular expression outcomes will involve several genomic approaches to measure gene expression and protein levels with the purpose of identifying candidate biomarkers that differ according to treatment group.

All continuous secondary and exploratory outcomes will be summarized and inspected for unusual outliers and distributional characteristics, and the treatment arms will be compared statistically using the nonparametric Wilcoxon rank sum test.

Analyses of secondary and exploratory endpoints and secondary analyses of the primary endpoint will be reported as exploratory.

10.4.3 Safety Analyses

Safety analyses will be restricted to the as-treated population and will include standard summary statistics and group comparisons (e.g., Chi square or Fisher's exact test) for adverse events, as well as lists of participant-level data where relevant. Time-to-event analyses will also be reported for select safety outcomes, for example for hospitalization, transplant or death, and certain serious adverse events, as well as treatment-related discontinuation. Methods for count data will be used for certain safety outcomes to compare treatment differences in number of events, such as number of respiratory exacerbations for respiratory cause.

10.4.5 Administrative Reporting

Administrative reporting will include accrual summaries and data completeness information according to site, losses to follow-up, measures of data timeliness by site, and other administrative measures if relevant. Administrative summaries will be pooled across treatment arms.

10.4.6 Trial Monitoring and Interim Analyses

Throughout the study, an external Data Safety Monitoring Board (DSMB) will review safety and administrative data periodically, according to the schedule specified in the DSMB Charter. Open session reports will summarize the following types of data: accrual, protocol deviations, data completeness, demographics and baseline characteristics, clinical and laboratory data, adverse events and other safety parameters, treatment compliance and dose modifications, reasons for treatment discontinuations, and causes of death. The open report will include analyses for all participants combined (i.e., pooled across treatment group). The closed report will present the data according to treatment group in a blinded fashion.

The trial is not designed to stop early for efficacy, thus preserving the 5% probability of a Type I error for the final analysis. The DSMB will review safety and administrative data to determine the safety and feasibility of continuing the trial. There exists a possibility that the DSMB will request additional participant-level data and/or recommend that the study stop temporarily or permanently for safety concerns that are set forth in the DSMB Charter or for administrative reasons such as slow accrual.

10.5 MEASURES TO MINIMIZE BIAS

10.5.1 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Neither site personnel (except for site research pharmacist(s) nor the participants will know which study treatment the participant is receiving. Pirfenidone and placebo will both be supplied in capsules that are visually indistinguishable. Pirfenidone and placebo packaging and labeling will be identical.

Participants will be randomized at Visit 2 (section 7.2.1) in a 1:1 ratio to receive either pirfenidone 2403 mg/d or placebo equivalent using automated web-based system. All randomization codes will be generated by a statistician independent of the trial conduct.

10.5.2 Unblinding of Treatment Assignment

The Sponsor (or designee) will prepare the randomization list. All subjects, monitors, and study center personnel related to the study, including the site pharmacist will be blinded to study treatment throughout the study. The randomization schema will be securely maintained electronically at the Data Coordinating Center.

If in the event of an emergency situation when knowledge of the treatment assignment will impact the clinical management of the subject, the investigator will have the ability to unblind the treatment assignment for that subject at any time. If a subject is unblinded by the investigator, the Sponsor must be informed of the unblinding within 24 hrs. If the blinding is prematurely broken, it is the responsibility of the investigator to promptly document and explain any unblinding to the Sponsor. Although all subjects will receive Pirfenidone or placebo during this study, breaking of the blind should not occur except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or when causality must be determined prior to submitting a regulatory safety report for a serious adverse event (SAE) (as defined in Section 8.2.2).

Any unblinding event carried out in connection with submission of a regulatory safety report will be conducted by the Sponsor.

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendix A – Schedule of Study Assessments) prior to unblinding, as knowledge of the treatment arm could influence subject assessment.

Following study completion, a letter will be sent to all participants to notify them of their assigned treatment group. Refer to Appendix D for a draft of the treatment assignment notification letter that will be given to the participants.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Every participating clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Participating clinical sites will also obtain institutional authorization for external monitoring by the Data Coordinating Center and the FDA to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are defined as all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source

documents when the data is collected and recorded there as the primary source of information, but CRFs will not constitute the only form of source document information for this trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The study will be monitored by clinical study monitors to assess adherence to good clinical practice (GCP) and to this clinical study protocol according to a Clinical Monitoring Plan.

The study may be audited by the sponsor's clinical quality assurance group to assess compliance with GCP (including but not limited to US Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) GCP guidelines, and other applicable regulations). Regulatory authorities, the IRB/IEC, and/or the sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audits or inspections. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This study will be conducted in compliance with GCP as described in FDA regulations (21 CFR parts 50, 54, 56, and 312) and the ICH document "Guideline for Good Clinical Practice, E6 (R1)," dated 10 June 1996. These practices are consistent with the principles stated in the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the US FDA). The study will also be carried out in keeping with local legal and regulatory requirements.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol and informed consent forms that will be used must be approved by the investigator's IRB/IEC before the study is initiated; documentation of this approval (i.e., a copy of the document showing IEC/IRB approval including the chairperson's signature and the date of approval) must be provided to the sponsors or designee and made available during an inspection by the US FDA or other regulatory agency inspectors.

Other investigator responsibilities regarding IEC/IRB requirements include the following:

- Submit to the IEC/IRB and to study sponsor or designee for review any advertisements that will be used to recruit patients
- During the conduct of the study, submit progress reports to the IEC/IRB, if required, and request
- Re-review of the study at least once a year
- Report, in writing, to the IEC/IRB any SAEs that occur during the study or SAEs reported in other studies using study treatment, per local IEC/IRB regulations
- Inform the IEC/IRB of any changes in the protocol and obtain documented IEC/IRB approval of the changes
- Provide the IEC/IRB with any other information it requests before or during the conduct of the study
- Maintain a file of study-related information, including all correspondence with the IEC/IRB
- Provide the IEC/IRB with a final report on the study within a time period consistent with local requirements

13.3 INFORMED CONSENT PROCESS

The investigator or designee is responsible for the content of the informed consent form, but the content must be approved by the IEC/IRB and sponsor or designee. The content of the informed consent must comply with FDA regulations (21 CFR 50.25) and the ICH document "Guideline for Good Clinical Practice, E6 (R1)," dated 10 June 1996. It should also include any additional information required by local laws relating to institutional review.

The investigator is responsible for obtaining informed consent from each patient participating in the study. If there are any amendments to the informed consent, patients should be consented properly in a timely fashion. All pertinent aspects of the study must be explained to the patient before he or she signs the informed consent form. Informed consent must be obtained from the patient before any Screening activity or treatment is undertaken that is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of the study treatment. Before a patient's participation in the study, the written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. The investigator is responsible for keeping this document in a secure place. This document should not be displayed or made accessible to any third party except the study sponsor or designee or regulatory agency representatives.

If a participant permanently revokes informed consent and declines further observation and Vital Status Assessments, then recording of study data will stop.

13.4 DELEGATION OF PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and any study-related duties. The investigator is responsible for assuring that study site staff are properly trained and credentialed to perform any delegated tasks.

13.5 COORDINATING INVESTIGATOR

The coordinating investigator will be one of the principal investigators on the study. The coordinating investigator will be responsible for signing the final clinical study report and assuring that the study has been executed according to the protocol.

14 DATA HANDLING AND RECORD KEEPING

14.1 RETENTION OF DOCUMENTS

The study-related records that must be maintained include the following:

1. Copies of the protocol and all amendments
2. Signed Principal Investigator Page for the protocol and all amendments
3. Initial Approval letter(s) from and all other correspondence to and from the IEC/IRB
4. Curricula vitae for the Principal Investigator and Sub-investigators
5. Documentation of study treatment shipments from Genentech or designee
6. Completed and signed dispensing records for study treatment

7. Documentation of unused study treatment destruction or return to Genentech or designee
8. Signed list of all study personnel including delegation of authority for all study personnel
9. Copy of the Investigator Brochure provided at start-up and subsequent versions for sites in the US. All other sites will maintain their regulatory authority's accepted, equivalent product safety document (ie. Summary of Product Characteristics (SmPC).
10. The original signed informed consent forms for each patient screened. Originals of all signed consent forms must be retained for all consent amendments for each randomized participant
11. Copies of eCRFs or electronic data capture data sets for each consented participant
12. Copies of results of all laboratory tests and other original data from which eCRF information was obtained as well as laboratory normal ranges and certifications, when indicated
13. Master Patient Log
14. Copies of all correspondence relating to this investigation

14.2 RETENTION OF DATA

The Principal Investigator must ensure that study data are accessible to the study sponsors or their representatives and to FDA or other regulatory agency inspectors. All study-related records (e.g., research charts, eCRFs, and other study records) must be retained until disposal is authorized by the study sponsors, which will be no sooner than 2 years after approval of the study agent for marketing in an ICH region (United States, Europe) and until there are no pending or contemplated marketing applications in an ICH region or 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents may need to be retained for longer periods in some countries due to local regulatory requirements.

14.4 INVESTIGATOR BROCHURE

The investigator will review the current version of the Investigator Brochure (IB). Sites outside of the U.S. may maintain their regulatory authority's accepted, equivalent product safety document (ie. Summary of Product Characteristics (SmPC). It is obligatory that the investigator be familiar with all sections of these documents before initiation of the study. These documents will be submitted to the IEC/IRB.

14.5 CASE REPORT FORMS

Each center will be instructed by the study sponsor or designee regarding how to record and complete electronic case report forms (eCRFs). Data should be recorded via eCRF as soon as possible after collection.

PFT, ECG, and central laboratory data should be reviewed, initialed, and dated by the principal investigator or designee. Completed eCRFs are to be reviewed by the investigator to ensure accuracy, completeness, and legibility within 2 weeks of last participant contact unless the forms are incomplete because of laboratory data or medical event follow-up that is not yet available.

14.6 PUBLICATION AND DATA SHARING POLICY

The study grantors will share authorship with investigators and their designees in any publications resulting from this study. Investigational plans, protocols, and data related to this study will be treated as confidential information. Before submission, the study grantors must review publication or presentation of data or information derived from this study.

15 STUDY ADMINISTRATION AND OVERSIGHT

15.1 PROCEDURE FOR PROTOCOL MODIFICATION

Modifications which may affect the safety of the study patient, or which may alter the scope of the investigation, the scientific quality of the study, the study design, dosages, duration of therapy, patient assessments (added evaluation that poses potential risk or inconvenience to the patient), number of patients, and/or patient eligibility criteria, may be made only after appropriate consultation between the investigators, the Study Executive Committee and the DSMB. Individual sites may not alter the protocol without advanced consultation and approval as noted here-in.

If the consensus is to revise the current protocol, a formal List of Changes will accompany the amended protocol and these will initially be submitted to the DSMB for review and until their recommendations for further modification have been addressed or it is approved. Once DSMB approval has been obtained, the revised Protocol and the List of Changes will be submitted to the FDA and to the IRBs at all participating clinical sites. Protocol changes will not be implemented until they have been reviewed and approved by all appropriate regulatory agencies and the study participants notified and/or their consent re-obtained if indicated by the nature of the requested change and the instructions of the FDA and/or responsible IRB.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 COVID-19 MANAGEMENT PLAN

The following changes have been made to the protocol in response to current COVID-19 pandemic recognizing the changes to the risk to participants in the study.

17.1 SAFETY CONCERN AND MANAGEMENT OF STUDY DRUG

Management and dispensing of study drug

- When subjects require study drugs, they should be mailed/shipped to the subject's home after completion of the required remote visit or as needed.
- Primary study outcome measures may need to be deferred based on changes to availability at individual sites during the COVID-19 pandemic. The study investigators will address these issues by modifying the analysis as necessary.
- Missing outcome data, which is a study deviation, should be noted in the site's study binder as due to "COVID-19 Restrictions". This will flag the reason as required for study audits.

17.2 IMPACT ON SCREENING AND RANDOMIZATION

New enrollments to the TRAIL 1 study will be placed on hold until further notice. This is a practical consideration given the growing international recommendation that all individuals at high risk, which include our study population, shelter in place and cease all non-essential activities. In addition, as the risk for potential COVID-19 infection rises, it is not appropriate to recommend that new participants start therapy when the threat from this virus is immediate and the potential benefit of therapy is unknown.
Each network leader can discuss with Dr. Ivan Rosas regarding the cessation of enrollment at their site.

17.3 MODIFICATIONS TO STUDY VISITS AND PROCEDURES

Conversion to remote study visits.

- Continued onsite visits **are not recommended or expected** at this time.
- Conversion to telehealth or video conferencing visits is acceptable as is contacting subjects by phone to conduct study visits. In most cases, local IRBs are accepting this conversion to remote visits without prior approval due to the urgent need to protect subjects.
- Efforts should be made to keep in contact with patients who are currently enrolled in the study through telemedicine and/or videoconferencing.

Schedule of Study Assessments edited for COVID-19.

- Visits 5 through 11 in the schedule of assessments can be converted to phone visits. There may be a reduction in the number of assessments, as not all will be feasible over the phone. If participants cannot be present for the visit, PFTs or Physical exam cannot be performed. The following assessments are categorized as the "expected assessments": Adverse events, Concomitant medication review, Supplemental oxygen review, Study medication dosing, Study medication accountability, Weight, Resting O2 Saturation, Patient questionnaire DAS 28 GH VAS, Patient GA, SGRQ, HAQ20, Dyspnea-12, LCQ, RAPID3, Vital status assessment.
- Monitoring of liver function testing should be continued as per protocol. If within the first 6 months of the study LFTs cannot be performed subjects should stop study treatment until labs can be obtained. Subjects are encouraged to continue the study visits.
- The subject is encouraged to restart study treatment when possible and appropriate.

- If the subject has interrupted study treatment for ≥28 days, a Pre-Restart Visit is required (Section 7.2.2). The Pre-Restart Visit will be conducted on the day study treatment is resumed. Subjects who restart study treatment will resume the visit schedule based on their date of randomization. If a regularly scheduled visit (Weeks 13, 26, 39, etc.) coincides with the Pre-Restart Visit, then the elements of the regularly scheduled visit as outlined above should be performed in lieu of the Pre-Restart Visit. Refer to Appendix B of the protocol on page 69 for re-titration.
- Visit window for visit 11 will be extended to +/- 4 weeks

17.4 SITE MONITORING

On-site monitoring visits will not be performed during COVID-19 pandemic. DCC will perform remote monitoring with source data verification as outlined in section 9 of the protocol. Regular monitoring visits will resume after travel restrictions have been lifted.

18 LITERATURE REFERENCES

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APPENDIX LIST

Version	Date	Description	Significant Revisions
		Appendix A - Schedule of Study Assessments	
		Appendix B - Capsule Dosing Flowchart	
		Appendix C- Safety Reporting Definitions and Contacts	
		Appendix D- Treatment Assignment Notification Letter	

Appendix A SCHEDULE OF STUDY ASSESSMENTS

	Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12			
	Visit Description	Screening Period	Eligibility and Random- ization	Telephone Assessment	Telephone Assessment	Protocol Visit	Protocol Visit	Protocol Visit	Lab Assessment	Protocol Visit	Protocol Visit	Protocol Visit	End of Study Phone Call	Pre-Restart	Unscheduled	Early Termination
	Week #	Week -8 to Week 0	Week 0	Week 1	Week2	Week 4	Week 8	Week 13	Week 19	Week 26	Week 39	Week 52	28 days after last dose of study drug	required if study tx was interrupted ≥28 days[13]		
Study Assessments	Visit Window	D-56 to D0	D1	± 2 days	± 2 days	± 1 week	± 1 week	± 2 weeks	± 1 week	± 2 weeks	± 2 weeks	± 1 week	± 1 week	N/A	N/A	N/A
Informed Consent		X														
Medical History / Review of Systems		X	X[7]													
Adverse Event Assessment		X	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Med Review		X	X[7]	X	X	X	X	X	X	X	X	X		X	X	X
Supplemental Oxygen Review		X	X[7]			X	X	X		X	X	X		X	X	X
Study Medication Dosing			X[9]	X	X	X	X	X		X	X	X		X[12]	X	X
Study Medication Accountability			X					X		X	X	X		X	X	X
Physical Exam		X	X[7]			X	X	X		X	X	X		X	X	X
Vital Signs (heart rate and blood pressure)		X	X[7]			X	X	X		X	X	X		X	X	X
Weight		X	X[7]			X	X	X		X	X	X		X	X	X
Height		X														
Lab Assessments[1]		X				X	X	X		X	X	X		X	X[14]	X
Liver Function Testing Only[11]									X							
Serologic tests[10]		X										X			X[14]	X
Pregnancy Test (blood)[2]		X	X[7]			X	X	X		X	X	X		X	X[14]	X
Biomarkers[16] (plasma, serum, and RNA)		X	X[7]			X		X		X	X	X				X
DNA Paxgene[17]			X[17]									X[17]				X
ECG		X[3]				X		X		X	X	X		X	X[14]	X
Resting Oxygen Saturation		X	X			X	X	X		X	X	X		X	X	X
Patient Questionnaires																
DAS 28 GH VAS			X									X				X
Patient GA			X					X		X	X	X				
Physician GA			X					X		X	X	X				
SGRQ			X					X		X	X	X				X
HAQ20			X					X		X	X	X				X
Dyspnea-12			X					X		X	X	X				X
Leicester Cough Questionnaire			X					X		X	X	X				X
RAPID3			X									X				X

Joint Count		X									X				X
Transbronchial biopsy or SLB (if avail)[15]	X														
HRCT scan	X[4]										X				X[18]
Spirometry	X[5]	X[7, 8]					X[8]		X[8]	X[8]	X[8]				X[8]
Lung volumes, DLCO or TLCO	X[6]										X				X
Confirmation of Eligibility		X[7]													
Randomization		X													
Vital Status Assessment			X	X								X			

[1] Lab Assessments include • Hematology (complete blood count with platelet count and automated differential) • Serum chemistry profile (albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, calcium, creatinine, glomerular filtration rate (eGRF), gamma-glutamyl transferase [GGT], glucose, potassium, sodium, BUN, uric acid and amylase)

[2] For women of childbearing potential

[3] Obtained before bronchodilator administration or on a separate day

[4] HRCT scans performed within 3 months of the Screening period may be used to confirm eligibility. Screening HRCT will be reviewed by a Central reader.

[5] FVC, FEV1 before and after bronchodilator administration

[6] obtained before or 30 min after bronchodilator administration

[7] Must be done prior to randomization

[8] without bronchodilator administration

[9] Instruct participant on dose titration and diary usage; 1st dose **must** be taken **in clinic** on day of randomization

[10] Serologic tests include: Erythrocyte Sedimentation Rate (ESR), Rheumatoid Factor (RF), C-Reactive Protein (CRP), and Cyclic Citrullinated Peptide (CCP)

[11] Liver Function Testing Only includes: AST, ALT, bilirubin, and alkaline phosphatase

[12] Instruct on re-titration of dose

[13] Participants who restart study treatment will resume the visit schedule based on their date of randomization. If a regularly scheduled visit (Weeks 13, 26, 39, etc.) coincides with the Pre-Restart Visit, then all of the elements of the regularly scheduled visit should be performed in lieu of the

[14] The elements of the visit are up to the discretion of the investigator.

[15] Surgical lung biopsy (SLB) or transbronchial biopsy, if performed, may be obtained up to 4 years before randomization

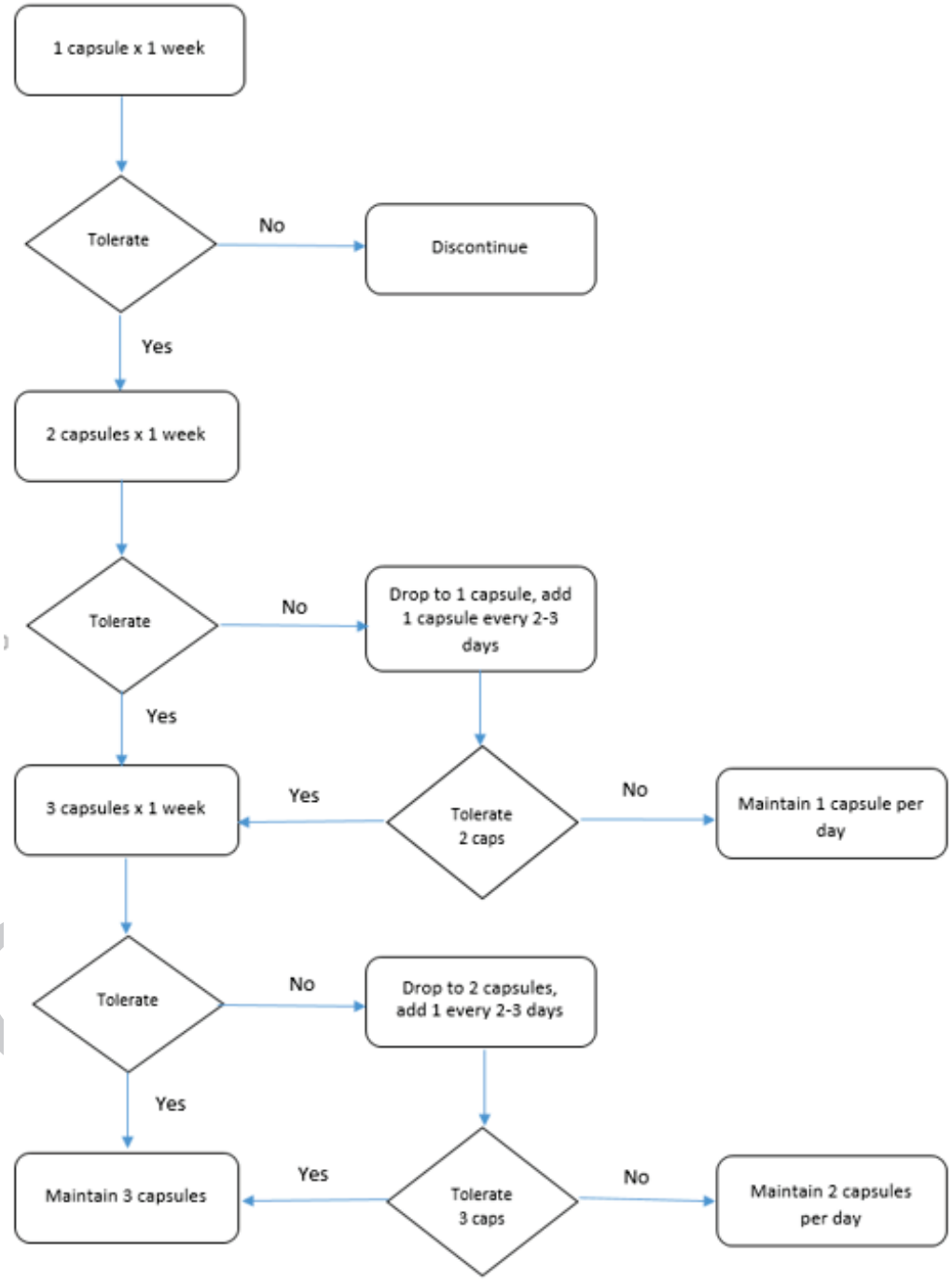
[16] RNA biomarker will only be collected at Visit 2(week 0) and Visit 11 (week 52) or Early Term

[17] DNA PaxGene samples are collected ONLY if subject consents to the genetic component of the study

[18] HRCT scans performed within the past 3 months will be acceptable

Appendix B TRAIL1 CAPSULE DOSING FLOWCHART

Dose reduction, interruption, and discontinuation of study drug to manage adverse events will be at the Investigators discretion. Subjects may be re-titrated over 2 weeks, once the symptoms have subsided. The below flow chart is provided as guidance for re-titration. The medical monitor is also available to discuss dose titration and management of adverse events.



Appendix C SAFETY REPORTING DEFINITIONS AND CONTACTS

The definitions below are based on the International Conference on Harmonization (ICH) guidelines and Food and Drug Administration (FDA) regulations. The use of italic font in this section refers to definitions taken from ICH guidelines and/or FDA regulations. Other definitions relate to company specific glossaries.

- Adverse Drug Reaction (ADR)
  In the pre-approval clinical experience or in other clinical trial experiences:

  Any noxious and unintended response to a medicinal product related to any dose will be considered an ADR.

  The phrase "responses to a medicinal product" or "associated with the use of the medication," means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

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

- Awareness Date
  The date any Party (including employees of affiliates or agents acting on behalf of either Party), first has knowledge of the minimum data elements as defined by ICH E2A guideline. At the very least, the following data must be provided for a case to be considered as valid:

  - an identifiable reporter*
  - an identifiable patient**(i.e., either CRF number, patient/subject number, initials, gender, date of birth, age or age group
  - a drug / counterfeit drug
  - an adverse event (or pregnancy)

  *For AE reports from social media sources, verified contact details (e.g., email address) are considered an identifiable reporter.

  **For reports from healthcare professionals, “a patient” is considered an identifiable patient criterion.

  The minimum data elements should be obtained initially prior to transmitting the information to the other Party. In the event that an AE/ADR or pregnancy report is lacking minimum data elements, this report should not be forwarded to the other Party until all the minimum data elements are gathered.

The originating Party will ensure prompt follow-up as necessary.

- Clinical Trial/ Study
  Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s), and/or to study absorption, distribution, metabolism and excretion of one or more investigational product(s) with the object of ascertaining their safety and/or efficacy.

- Development Safety Update Report (DSUR)
  A comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether marketed or not. The main objective of a DSUR is:
  - Assess whether the information obtained by the Sponsor during the reporting period is in accord with previous drug safety knowledge
  - Describe new safety issues that could have an impact on the protection of clinical trial subjects
  - Summarize the current understanding and management of identified an potential risks
  - Provide an update on the status of the clinical investigation/development program and study results.

- European Medicines Agency (EMA)
  The centralized European regulatory authority for the European Union (EU) member states.

- European Economic Area (EEA)
  European Union (EU) plus Iceland, Liechtenstein and Norway.

- Expedited Safety Report
  A single case report requiring submission to any regulatory authority within 7 and/or 15 calendar days.

- Food and Drug Administration (FDA)
  US Federal Agency charged with the responsibility of enforcing the Federal Food, Drug and Cosmetic Laws and Regulations.

- International conference on Harmonization (ICH)
  International Conference on Harmonization of Technical Requirements for Registration on Pharmaceuticals for Human Use.

- Investigational Medicinal Product (IMP)
  A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

- Non-Serious Adverse Event
  Any event that does not meet the definition of serious as defined below under SAE/SADR.

- Product
  The Roche product that is the subject of the trial/study as defined in the corresponding agreement.

- Reference safety information (RSI)
  Depending on the development and marketing status of the drug, the Reference Safety Information (RSI) may be one or more of the following:

  - Core Data Sheet (CDS)
  - Summary of Product Characteristics (SPC)
  - Investigator's Brochure
  - International Standard Prescribing Information (ISPI)
  - Local Label, e.g., United States Package Insert (USPI)

- Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)
  A serious adverse event (experience) or reaction is any untoward medical occurrence or effect that at any dose:

  - results in death
  - is life-threatening

Note: The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above).

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

In certain protocols, specific arrangements may be made for SAE reporting (e.g., efficacy end points, study, specific events) which are not reported as SAEs to regulatory authorities during a clinical trial. Details of these should be documented and made known to either Party.

- Single case reports
  A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe adverse events following the administration of one or more medicinal products to an individual patient at a particular point of time.

- Six Monthly SUSAR Report
  SUSAR report for an Investigational Medicinal Product (IMP) containing a listing of all SUSARs for a defined six monthly period providing a brief summary of any safety-related issues for that IMP.

- Sponsor

  ICH E6:

  An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

CFR 312.3:

A person who takes responsibility for and initiates a clinical investigation. The Sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

- SUSAR
  Suspected Unexpected Serious Adverse Reaction.

- Unexpected Adverse Drug Reaction
  An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved Investigational Medicinal Product or package insert/summary of product characteristics for a marketed medicinal product).

Roche Contacts

Activity	Person Responsible
General Queries/ Aggregate Reports (e.g., DSUR, Line-listings of Non-serious AEs)	Drug Safety Contact Line Mailbox: contact_line.drug_safety@roche.com
Single Case Management	**Single case reports to Roche:** Central Operations Mailbox: welwyn.pds-pc@roche.com Fax (Clinical): +44 1707 377 967/ 373 779/ 373 793/ 390 959 Fax (Spontaneous): +44 1707 390 904 **Queries on Single Case Reports/Case Transmission Verification:** Safety Operations Contact Line Mailbox: welwyn.contact_line_rce@roche.com **Cc:** Ivan O. Rosas Study Principal Investigator Baylor College of Medicine7200 Cambridge Street Houston, TX 77030 **For US IIS only:**

BCM Contacts

Activity	Person Responsible
Single Case Management, Safety Crisis Management, Aggregate Safety Reports	Ivan O. Rosas Pulmonary Critical Care and Sleep Medicine Baylor College of Medicine 7200 Cambridge Street Houston, TX 77030 Tel: (713)-798-8842 Fax: (713) 798-2688 Ivan.Rosas@bcm.edu

Appendix D **TREATMENT ASSIGNMENT NOTIFICATION LETTER**

__/__/__

Dear (participant name),

Thanks to the hard work and commitment of the investigators, coordinators and, *study participants like you*, the TRAIL1 study has been successfully completed. Not only did your participation contribute important information for testing a new treatment, but it will also continue to help us learn more about Rheumatoid Arthritis Interstitial Lung Disease as we perform additional analyses of the data and samples collected during the TRAIL1 study.

We want to take this opportunity to tell you whether you were taking Pirfenidone or placebo during the TRAIL1 study. Through the randomization process, your drug assignment was __ *Pirfenidone* or *Placebo* ___.

We will post the publications related to TRAIL1 study that describes the study results on the TRAIL1 website once it is published.

Once again, we would like to convey our sincere appreciation for your participation. We cannot thank you enough for all the time you have put into this study. We truly could not have done this without you!

Please let us know if you have any questions.

With warmest wishes and great gratitude,

(Signatures)

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