Official Title: **MULTICENTER, INTERNATIONAL, DOUBLE-BLIND, TWO-ARM, RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL OF PIRFENIDONE IN PATIENTS WITH UNCLASSIFIABLE PROGRESSIVE FIBROSING ILD**

NCT Number: NCT03099187

Document Date: Protocol Version 3: 28-June-2018

PROTOCOL

TITLE:	**MULTICENTER, INTERNATIONAL, DOUBLE-BLIND, TWO-ARM, RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL OF PIRFENIDONE IN PATIENTS WITH UNCLASSIFIABLE PROGRESSIVE FIBROSING ILD**
PROTOCOL NUMBER:	MA39189
VERSION NUMBER:	3.0
EUDRACT NUMBER:	2016-002744-17
IND NUMBER:	67284
TEST PRODUCT:	Pirfenidone (RO0220912)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1.0: 15 November 2016
DATE AMENDED:	Version 2.0: 03 March 2017 Version 3.0: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	28-Jun-2018 12:58:04

PROTOCOL AMENDMENT No. 2.0, PROTOCOL VERSION 3.0: RATIONALE

Protocol version 2.0 has been amended mainly in order to provide additional guidance on trial specific procedures. Changes to the protocol including the rationale for each change are listed below.

- Synopsis (Target Population) and Protocol Section 4.1 (Patients) of the protocol have been amended in order to provide guidance on conditions for allowing the re-screening of patients.
- Protocol Section 4.5.5 (FVC) has been amended to provide guidance on when to use a short-acting bronchodilator prior to on-site spirometry for patients who are routinely treated with such medication.
- Protocol Sections 4.5.9 (Electrocardiograms) and 5.1.1.8 (Management of Increases in QT Interval) have been amended to provide more clear guidance for ECGs and the management of increases in QT interval.
- Protocol Section 4.5.10 (Patient-Reported Outcomes) has been amended as the timing for the completion of the Patient-Reported Outcomes is independent of the administration time of the trial treatment.
- Protocol Section 4.6.1 (Patient Discontinuation) has been amended to include lung transplantation during the trial as a reason for patient discontinuation.
- Schedule of Assessments has been amended to reflect the changes made to the body of the protocol and also to provide further trial-specific guidance.

Additional minor changes have been made to improve clarity and consistency. New information is shown in italics and deletions to text are shown as strikethrough. This amendment represents cumulative changes to protocol version 2.0.

PROTOCOL AMENDMENT No. 2.0, PROTOCOL VERSION 3.0:
SUMMARY OF CHANGES

GLOBAL CHANGES

Protocol version 2.0 (3 March 2017) has been amended in order to provide further guidance on trial specific procedures.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes made to the protocol, where applicable.

SECTION: Target Population

Reason for change: Text has been added to provide guidance on conditions allowing for the re-screening of patients.

Added text:

Re-screening may be considered for patients who do not show sufficient disease deterioration in accordance to the protocol at the time of the initial screening. Re-screening is permitted if there is strong evidence of clinical worsening based on the Investigator's judgement and only upon receipt of official approval from the Study Management Team. In such cases, re-screening may be performed after a minimum of 4-weeks lapse from the initial screening date.

PROTOCOL

SECTION 4.1: Patients

Reason for change: Text has been added to provide guidance and conditions allowing for the re-screening of patients.

Added text:

Re-screening may be considered for patients who do not show sufficient disease deterioration in accordance to the protocol at the time of the initial screening. Re-screening is permitted if there is strong evidence of clinical worsening based on the Investigator's judgement and only upon receipt of official approval from the Study Management Team. In such cases, re-screening may be performed after a minimum of 4-weeks lapse from the initial screening date.

SECTION 4.5.5: FVC

Reason for change: Text has been added in order to provide additional guidance on the use of short-acting bronchodilator prior to spirometry.

Added text:

If a patient is routinely treated with a short-acting bronchodilator (for example albuterol, salbutamol), the bronchodilator should be taken approximately 30 minutes prior to the on-site spirometry.

SECTION 4.5.9: Electrocardiograms

Reason for change: Text amended in order to replace a general guidance with specific requirements provided in section 5.1.1.8.

Amended text:

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent trial file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and the QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory. *Refer to section 5.1.1.8 for details on protocol management of increases in QT interval.*

~~If at a particular post-dose time point the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted at the discretion of the investigator. A decision on trial treatment discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, and severe bradycardia).~~

SECTION 4.5.10: Patient-Reported Outcomes

- **Reason for change:** Text has been amended as the timing for the completion of the Patient-Reported Outcomes is independent of the administration time for the trial treatment.

Amended text:

PRO data will be collected via questionnaires to document the treatment effect and to evaluate the benefit of pirfenidone. The questionnaires, translated into the local language as required, will be completed in their entirety at specified time points during the trial (see Appendix 1) To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status~~,~~ *and* prior to the performance of non-PRO assessments~~, and prior to the administration of trial treatment,~~ unless otherwise specified.

SECTION 4.6.1: Patient Discontinuation

Reason for change: Text has been amended in order to include lung transplantation as reason for patient's discontinuation from the trial.

Added text:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the trial
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as non-adherence with the dosing regimen, including the dose-titration guidance for starting trial treatment
- *Lung transplantation*

Patients who undergo lung transplantation during the trial will be discontinued at the time of hospitalization for transplantation.

SECTION 5.1.1.8: Management of Increases in QT Interval

Reason for change: Text has been amended in order to provide more clear guidance on the management of increases in QT interval.

Amended text:

~~In the event of a QTcF interval >550 ms or an increase from baseline of >60 ms, a repeat ECG must be obtained within 24 hours. If the QTcF finding is confirmed by the repeat ECG and verified by the site (trial center) or local cardiologist, pirfenidone treatment should be discontinued and the patient should be withdrawn from the trial.~~

In the event of a QTcF interval of ≥500~~ 550~~ ms or an increase from baseline of 31-60 ms, a repeat ECG must be obtained within 24 hours. If the QTcF finding is confirmed by the repeat ECG and verified by the site *(trial center)* or local cardiologist, pirfenidone treatment should be *discontinued and a decision on trial treatment discontinuation should be made, as described in Section 4.6.1* ~~interrupted~~.[…]

SECTION 5.4.4: Reporting Requirements for Cases of Pirfenidone Accidental Overdose, Medication Error, Drug Abuse, or Drug Misuse

Reason for change: Text has been amended in order to include new requirements for safety reporting related to overdose, medication error, drug abuse, or drug misuse.

Added text:

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm

- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For Pirfenidone, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with Pirfenidone, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.

• Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

APPENDIX 1: Schedule of Assessments

Guidance Text

Reason for change: Guidance text amended as the timing of the trial visit assessments is independent of the administration time for the trial treatment.

Amended text:

Notes: all assessments should be performed within 7 days of the scheduled visit, unless otherwise specified. ~~On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.~~

Foot Note C

Reason for change: Guidance text amended as during the first 6 months of the 12-month open-label period, trial visits are conducted on a monthly basis.

Amended text:

[c] After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. *During the 12-month safety follow-up period, initially, patients will be evaluated at monthly visits for the first 6 months. At the end of the first 6 months, patients will be evaluated at each site visit occurring approximately every 3 months until the end of the safety follow-up period.* ~~During the safety follow up period, the patients should be evaluated by the investigator approximately every 3 months.~~ […]

Foot Note Q

Reason for change: Guidance text amended as the timing of the trial visit assessments is independent of the administration time for the trial treatment.

Amended text:

[q] Questionnaires will be self-administered prior to the patient receiving any information on disease status *and*~~,~~ prior to the performance of non-PRO assessments~~, and prior to the administration of trial treatment~~. […]

Foot Note U

Reason for change: Guidance text added for patients who discontinue the trial between weeks 24 and 28 and which visit assessments should be conducted as the final visit.

Amended text:

[U] If a patient discontinues the trial between weeks 24 and 28, final assessments according to the Follow-up visit for week 28 should be performed.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**MULTICENTER, INTERNATIONAL, DOUBLE-BLIND, TWO-ARM, RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL OF PIRFENIDONE IN PATIENTS WITH UNCLASSIFIABLE PROGRESSIVE FIBROSING ILD**
PROTOCOL NUMBER:	MA39189
VERSION NUMBER:	3.0
EUDRACT NUMBER:	2016-002744-17
IND NUMBER:	67284
TEST PRODUCT:	Pirfenidone (RO0220912)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your site contact.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

TITLE:	**MULTICENTER, INTERNATIONAL, DOUBLE-BLIND, TWO-ARM, RANDOMIZED, PLACEBO-CONTROLLED PHASE II TRIAL OF PIRFENIDONE IN PATIENTS WITH UNCLASSIFIABLE PROGRESSIVE FIBROSING ILD**
PROTOCOL NUMBER:	MA39189
VERSION NUMBER:	3.0
EUDRACT NUMBER:	2016-002744-17
IND NUMBER:	67284
TEST PRODUCT:	Pirfenidone (RO0220912)
PHASE:	II
INDICATION:	Fibrotic interstitial lung disease of unknown origin
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This trial will evaluate the efficacy and safety of pirfenidone in patients with fibrosing interstitial lung disease (ILD) who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary team (MDT) review ("unclassifiable" ILD).

Efficacy Objective

The primary efficacy objective for this trial is to evaluate the effect of pirfenidone vs. placebo on lung function parameters on the basis of the following endpoint:

- Rate of decline in forced vital capacity (FVC) measured in mL by daily handheld spirometer over the 24-week double-blind treatment period.

Safety Objective

The safety objective for this trial is to evaluate the safety of pirfenidone vs. placebo on the basis of the following endpoints:

- Nature, frequency, severity, and timing of treatment-emergent adverse events
- Dose reductions and treatment interruptions
- Clinical laboratory test results
- 12-lead electrocardiograms (ECGs)
- Withdrawals from trial treatment or trial discontinuations.

Exploratory Objective

One exploratory objective for this trial is to evaluate the role of MMF (mycophenolate mofetil/sodium or mycophenolic acid) treatment in ILD on the basis of the following endpoint:

- Efficacy and safety data from subgroups of patients who did or did not receive MMF treatment.

In addition, exploratory biomarkers associated with fibrosis and ILD will be evaluated in plasma, serum, and whole blood ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) samples.

Trial Design

Description of Trial

This is a multicenter, international, double-blind, two-arm, randomized, placebo-controlled Phase II trial in patients with fibrosing ILD who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by MDT review ("unclassifiable ILD"). Patients will be randomized in a 1:1 ratio, on a double-blind basis using a stratified algorithm, to receive either pirfenidone (801 mg three times daily [TID]) or placebo. The randomized patients will be stratified by concomitant MMF treatment (yes/no), the presence/absence of interstitial pneumonia with autoimmune features (IPAF) as defined by the MDT.

Most established MDTs have access to clinical, radiologic, and pathology expertise, and should have a sufficient case load of ILDs per year. Access to rheumatology expertise will be at the discretion of the MDT.

In total, approximately 90 clinical centers (sites) in Australia, Europe, the Middle East, and North America are expected to enroll approximately 250 patients. Patients who are withdrawn from the trial will not be replaced. The trial design is represented in Figure 1.

After discussing the risks and benefits of the trial with the investigator and providing informed consent, patients will be required to taper and/or discontinue all prohibited medications (Section 4.4.2) in the 28 days prior to the start of screening during the washout period. If a prohibited medication must be tapered, the process must start early enough so that the patient discontinues the medication in the 28 days prior to the start of screening. After completing the washout period, patients will enter screening, which lasts up to 21 days. During screening, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. Patients not taking a prohibited medication will forgo the washout period and directly enter screening.

At the end of screening, patients will be randomized (Day 1) to receive either pirfenidone or placebo (1:1 ratio).

Following treatment initiation, the daily dosage will be titrated to the full dosage of nine capsules per day over a 14-day period as outlined in Table 2 . After the titration period, trial treatment will continue through Week 24 and monitoring will be conducted by trial visits. Patients should remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced or dosing is interrupted to manage an adverse event (see Section 5.1.1). Any patient with an actual or anticipated interruption of trial treatment for a period of ≥28 consecutive days will be reported by telephone to Roche's medical monitor or designee to discuss the circumstances of the case. Once the patient restarts trial treatment, the dose must be re-titrated over 14 days as described in Table 2 . A Follow-up Visit will occur 28 days after the end of the 24-week double-blind treatment period.

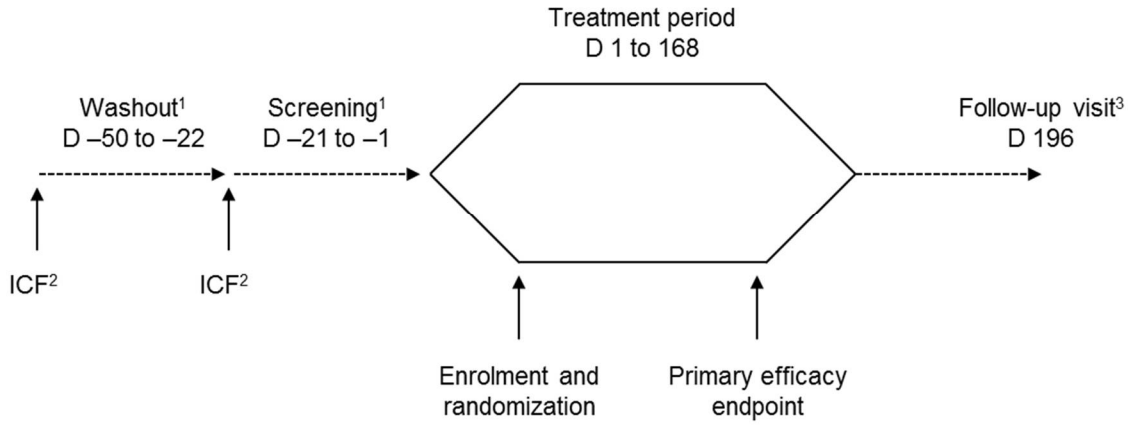
After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the safety follow up period, the patients should be evaluated by the investigator initially at monthly visits during the first 6 months and subsequently at each visit occurring approximately every 3 months thereafter. A final Follow-up Visit will be performed at the end of the safety period, 28 days after the last open-label dose.

Table 1 Titration Schedule

Treatment Days	Dosage
Days 1 through 7	One capsule three times daily with meals
Days 8 through 14	Two capsules three times daily with meals
Day 15 onwards	Three capsules three times daily with meals

The Sponsor will provide trial treatment on a double-blind basis. The design that will be utilized in this trial is shown in Figure 1.

Figure 1 Trial Schema



[1] Patients will be required to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period. Patients not taking a prohibited medication will forgo the washout period and directly enter screening.

[2] Informed consent must be documented before any trial-specific screening procedure is performed, and may be obtained either at the Washout or Screening Visits.

[3] After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final Follow-up Visit will be performed at the end of the safety period, 28 days after the last open-label dose.

D=Day; ICF=informed consent form

The primary objective of this trial is to evaluate the efficacy of pirfenidone vs. placebo on lung function parameters by examining the rate of decline in FVC (measured in mL). A handheld spirometry device will be used by the patient to measure daily FVC at home. Confirmatory site (trial center) based FVC measurements will be conducted every 4 weeks (see Schedule of Assessments; Appendix 1). Blood samples will be obtained from patients in order to analyze clinical laboratory values and biomarkers.

Number of Patients

Approximately 250 patients with unclassifiable fibrosing ILD will be enrolled in this trial.

Target Population

Inclusion Criteria

Patients must meet the following criteria for trial entry:

1. Signed Informed Consent Form
2. Age ≥18–85 years
3. Able to comply with the trial protocol, according to the investigator's judgment
4. Confirmed fibrosing ILD which, following MDT review, cannot be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD (e.g. chronic hypersensitivity or connective tissue disease-ILD [CTD-ILD])
5. Progressive disease as considered by the investigator using the following definition:
    a. Patient deterioration within the last 6 months, which is defined as:
        i. A rate of decline in FVC >5% OR
        ii. Significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes.
6. Extent of fibrosis >10% on high-resolution computed tomography (HRCT; visual scoring) within the last 12 months
7. FVC ≥45% of predicted value
8. Diffusing capacity of the lung for carbon monoxide (DLco) ≥30% of predicted value
9. Forced expiratory volume in 1 second (FEV_1)/FVC ratio ≥0.7
10. 6-minute walk distance (6MWD) ≥150 meters
11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1% per year during the treatment period and for at least 58 days after the last dose of trial treatment:
    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, hormonal contraceptives including those 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.

    For men: 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 trial treatment. Men must refrain from donating sperm during this same period
    b. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 118 days after the last dose of trial treatment to avoid exposing the embryo

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.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

1. Diagnosis with moderate or high confidence of nonspecific interstitial pneumonia (NSIP) and any ILD with an identifiable cause such as CTD-ILD, chronic hypersensitivity pneumonitis (cHP), or others
2. Diagnosis of idiopathic pulmonary fibrosis (IPF) independent of the confidence level
3. History of unstable angina or myocardial infarction during the previous 6 months
4. Pregnant or lactating, or intending to become pregnant during the trial
5. A positive urine pregnancy test, which was confirmed with a positive serum pregnancy test. Women with a confirmed pregnancy will be excluded from trial participation and must discontinue trial treatment
6. Treatment with high dose systemic corticosteroids (i.e., >15 mg/d of prednisolone or equivalent), or any immunosuppressant other than MMF, at any time at least 4 weeks prior to screening. Patients being treated with MMF should be on a stable dose that is expected to remain stable throughout the trial and was started at least 3 months prior to screening
7. Patients previously treated with pirfenidone or nintedanib
8. Patients treated with N-acetyl-cysteine (NAC) for fibrotic lung disease, at any time within the 4 weeks of the screening period
9. Drug treatment for any type of pulmonary hypertension (e.g. sildenafil, endothelin receptor antagonist [ERA], etc.)
10. Participation in a trial of an investigational medical product within the last 4 weeks
11. Significant co-existent emphysema (extent greater than extent of fibrosis on HRCT within the last 12 months)
12. Significant other organ co-morbidity including hepatic or renal impairment
13. Previous intolerance or allergy to the trial treatment
14. Pregnant patients, or women of child-bearing potential, not using a reliable contraceptive method
15. Unable to provide informed written consent
16. Predicted life expectancy <12 months or on an active transplant waiting list
17. Use of any tobacco product in the 12 weeks prior to the start of screening, or any unwillingness to abstain from their use through to the Follow-up Visit
18. Illicit drug or alcohol abuse within 12 months prior to screening, according to the investigator's judgment
19. Planned major surgery during the trial
20. Hypersensitivity to the active substance or to any of the excipients of pirfenidone
21. History of angioedema
22. Concomitant use of fluvoxamine
23. Clinical evidence of any active infection which according to the investigator's judgment may interfere with trial conduct, measurement of pulmonary function, or impact the course of the ILD

24. Any history of hepatic impairment, elevation of transaminase enzymes, or the confirmation of any of the following liver function test (LFT) criteria above the specified limits:
    a. Total bilirubin above the upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × ULN
    c. Alkaline phosphatase >2.0 × ULN.
25. Creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault formula
26. Any serious medical condition, clinically significant abnormality on an ECG at screening, or laboratory test results (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk to the patient following the administration of trial treatment
27. An ECG with a heart rate corrected QT interval (corrected using Fridericia's formula [QTcF]) ≥500 ms at screening, or a family or personal history of long QT syndrome.

Re-screening may be considered for patients who do not show sufficient disease deterioration in accordance to the protocol at the time of the initial screening. Re-screening is permitted if there is strong evidence of clinical worsening based on the Investigator's judgement and only upon receipt of official approval from the Study Management Team. In such cases, re-screening may be performed after a minimum of 4-weeks lapse from the initial screening date.

End of Trial and Length of Trial

After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. The end of the clinical trial is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point which is required for the statistical analysis is received, whichever is the later date. For this trial, LPLV will occur when the last patient has completed the final safety Follow-up Visit, 28 days after the final open-label dose, or when the last data point is collected in the safety follow-period.

For each patient the total length of the trial is expected to be up to a maximum of 91 weeks. The trial duration includes the washout period of up to 4 weeks, the screening period of up to 3 weeks, the double-blind treatment period of 24 weeks, the follow-up period of 4 weeks, the open-label safety follow-up period up to 12 months (52 weeks) and a final safety Follow-up Visit 4 weeks after the last dose.

Investigational Medicinal Products

Pirfenidone and Placebo

Pirfenidone and placebo will be supplied by the Sponsor as 267 mg capsules in a bottle. For information on the formulation and handling of pirfenidone, see the Investigator's Brochure or local prescribing information for pirfenidone.

Placebo will be supplied by the Sponsor in the form of capsules with identical appearance and size as the pirfenidone capsule. The placebo capsules will contain microcrystalline cellulose.

Statistical Methods

Primary Analysis

The primary efficacy objective for this trial is to evaluate the efficacy of pirfenidone vs. placebo on lung function parameters on the basis of rate of decline in FVC in mL

measured by handheld spirometry over the 24-week double-blind treatment period (see Section 2).

The primary analysis will be based on the intent-to-treat (ITT) population. Patients who discontinue treatment prematurely will be analyzed based on the available data. No imputation method will be applied.

The primary analysis of the primary endpoint will compare the mean FVC decline in each treatment arm using a student's t-test with a two-sided significance level $\alpha=0.05$. The mean FVC decline for each treatment arm will be calculated using the estimated FVC decline for each individual patient. The individual FVC decline will be estimated by applying a linear regression model to all data points collected during the 24-week double-blind treatment period.

Determination of Sample Size

The purpose of this trial is hypothesis generation regarding the efficacy of pirfenidone vs. placebo on lung function parameters on the basis of rate of decline in FVC, as measured by daily handheld spirometry.

A total sample size of approximately 250 patients is planned, and patients will be randomized in a 1:1 ratio. The randomization will be stratified by concomitant MMF treatment (yes/no), the presence/absence of IPAF as defined by the MDT.

The planned sample size is based on the statistical hypothesis of the primary endpoint and assumes 80% power and a two-sided significance level of 5% using a student's t-test. It is assumed, after inspection of historical data, that FVC decline in the placebo arm is 85 mL with a common standard deviation of 70 mL, which can be reduced to 60 mL with a common standard deviation of 70 mL in the pirfenidone arm. In this scenario, 125 patients per treatment arm are needed to detect this treatment effect with 80% power.

Interim Analyses

There are no planned interim efficacy analyses for this trial. Safety interim analyses will be performed at least three times during the trial, at approximately 6, 12, and 18 months after the start of recruitment.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWD	6-minute walk distance
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	two times daily
BTPS	body temperature and pressure saturated with water vapor
BUN	blood urea nitrogen
CAPACITY	Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes
cHP	chronic hypersensitivity pneumonitis
CI	confidence interval
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTD	connective tissue disease
CYP	cytochrome P450
DLco	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EEA	European Economic Area
ERA	endothelin receptor antagonist
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computed tomography
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IL	interleukin

Abbreviation	Definition
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
IPAF	interstitial pneumonia with autoimmune features
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LFT	liver function test
LOTUSS	An open-Label, randOmized, Phase 2 sTUdy of the safety and tolerability of pirfenidone when administered to patients with Systemic Sclerosis−related interstitial lung disease
LPLV	last patient, last visit
MDT	multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil/sodium or mycophenolic acid
NAC	N-acetyl-cysteine
NCI	National Cancer Institute
NGS	next-generation sequencing
NSIP	nonspecific interstitial pneumonia
PDGF	platelet-derived growth factor
PFS	progression-free survival
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RBR	Research Biosample Repository
RNA	ribonucleic acid
SAP	Statistical Analysis Plan
SGRQ	St. George's Respiratory Questionnaire
SOBQ	Shortness of Breath Questionnaire
SOC	System Organ Class
SSc	systemic sclerosis
TGF	transforming growth factor
TID	three times daily
UCSD	University of California, San Diego
UIP	usual interstitial pneumonia

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VC	vital capacity
WBC	white blood cell
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON UNCLASSIFIABLE INTERSTITIAL LUNG DISEASE

The proper classification of interstitial lung diseases (ILDs) requires multidisciplinary expertise with input from various clinical experts, including pulmonologists, thoracic radiologists, and lung pathologists (Ryerson et al. 2013). Despite this coordinated effort, approximately 15% of all patients evaluated by multidisciplinary teams (MDTs) cannot ultimately be classified according to their fibrosing ILD (Skolnik and Ryerson 2016). Classification cannot be achieved in these patients due to nonspecific or conflicting clinical, radiological, or histopathological findings, or because patients are unable or unwilling to undergo certain, in particular invasive, diagnostic procedures (Cottin and Wells 2013; Ryerson et al. 2013).

Unclassifiable ILD represents a heterogeneous collection of undiagnosed fibrosing ILDs, which have a prognosis between idiopathic pulmonary fibrosis (IPF) and other non-IPF fibrosing ILDs (Ryerson et al. 2013). Patients also display clinical features typical of both IPF, dominated by fibrotic changes to lung architecture, and other non-IPF ILDs (i.e., chronic hypersensitivity pneumonitis [cHP], idiopathic nonspecific interstitial pneumonia [NSIP], connective tissue disease-ILD [CTD-ILD]), in which inflammatory processes predominate. The fibrotic features of IPF include the patchy involvement of lung parenchyma by fibrosis/architectural distortion, honeycombing in a predominantly subpleural/paraseptal distribution, and the presence of fibroblast foci (Spagnolo et al. 2012). Owing to the heterogeneous nature of the disease, the choice of pharmacotherapy for unclassifiable ILD is unquestionably complex (Skolnik and Ryerson 2016). Treatment usage is complicated by both a lack of direct evidence in this patient population and by clinical data that indicate that different therapeutic strategies need to be employed in patients with IPF compared with patients with other fibrotic ILDs (Raghu et al. 2012; Skolnik and Ryerson 2016). Therefore it is not currently possible to use one specific therapy in all patients with unclassifiable ILD and each patient must be treated on a case-by-case basis (Skolnik and Ryerson 2016).

Although no specific therapy has been universally recommended to treat patients with unclassifiable ILD, immunomodulatory treatments such as mycophenolate mofetil (MMF) have been used by several authors to treat the diverse spectrum of ILD (Fischer et al. 2013; Panopoulos et al. 2013; Tzouvelekis et al. 2012).

1.2 BACKGROUND ON PIRFENIDONE

Pirfenidone is an orally active, small molecule (molecular weight: 185.2 g/mol) that has been shown to exert both antifibrotic and anti-inflammatory properties in a variety of animal models and *in vitro* systems. The broad antifibrotic activity of pirfenidone across organ systems has been demonstrated in more than 20 animal studies utilizing various models that examined liver, heart, kidney, and lung fibrosis (Schaefer et al. 2011). Studies involving bleomycin-induced pulmonary fibrosis models found that pirfenidone

reduced visible lung pathology, lung tissue hydroxyproline content, edema (wet-to-dry lung weight), as well as the histological fibrotic score (Oku et al. 2008; Takeda et al. 2014). Additionally, pirfenidone administration significantly suppressed bleomycin-induced increases in interleukin- (IL)-1β, IL-6, monocyte chemoattractant protein-1, and IL-12p40 in these models (Oku et al. 2008).

In cell-based systems, pirfenidone suppressed the proliferation of fibroblasts; attenuated the production of profibrotic cytokines, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β); promoted the release of collagenase from fibroblasts; and reduced the accumulation of certain extracellular matrix components, in particular collagen (EMA 2010).

Taken together, the preclinical cell-based studies and the investigations involving animal fibrosis models provide evidence that pirfenidone reduces levels of profibrotic growth factors and cytokines, lessens collagen deposition, and reduces interstitial fibrosis. All of these factors are known to be physiological elements which are to dysregulated in IPF (Clarke et al. 2013; Ryu et al. 2014; Todd et al. 2012).

Following on from the promising findings obtained in the extensive pre-clinical program, several clinical trials were conducted to investigate the efficacy and safety of pirfenidone in patients with IPF. A proof-of-concept study in 107 patients with IPF found that treatment with pirfenidone improved vital capacity (VC) and prevented acute exacerbation of IPF during the 9 months of follow-up (Azuma et al. 2005). Although significant adverse events were associated with pirfenidone, treatment adherence was similar between the pirfenidone and placebo groups. In fact, the study was aborted early on the basis of recommendations from the Data and Safety Monitoring Board (DSMB) in favor of pirfenidone treatment over placebo. Building on the results of this study, the Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) program included two similar multinational Phase III trials and was designed to confirm the effects of pirfenidone on reducing the decline in lung function (Noble et al. 2011). Pirfenidone significantly reduced the decline in forced vital capacity (FVC) in one study (Study 004), although the difference between pirfenidone and placebo in FVC change was not significant at Week 72 in the other trial (Study 006). Patients in the pirfenidone group experienced higher rates of several adverse events, including nausea, rash, and vomiting, although fewer overall and deaths related to IPF occurred in the pirfenidone group. Agreeing with the results of Study 004, a further Phase III study in 275 Japanese patients found that treatment with pirfenidone decreased the rate of decline in VC and increased the progression-free survival (PFS) time over 52 weeks (Taniguchi et al. 2010). Owing to the discrepancies between the results of the three Phase III trials, a further subsequent trial was initiated to confirm the beneficial effect of pirfenidone on disease progression in patients with IPF (King Jr. et al. 2014). This trial enrolled 555 patients with IPF and found that pirfenidone reduced disease progression, as reflected by reduced declines in lung function and exercise

tolerance, and improved PFS. Pirfenidone treatment was also associated with an acceptable side-effect profile and fewer deaths compared with placebo.

Following on the positive clinical results achieved, pirfenidone was approved in a 267 mg capsule dosage form for the treatment of IPF in the United States (US), and for the treatment of mild to moderate IPF in the European Economic Area (EEA) and Canada (Esbriet SmPC 2015; Health Canada 2016; US FDA 2015). The recommended daily maintenance dose in patients with IPF is 2403 mg/d, administered as three 267 mg capsules (801 mg) three times daily (TID) with food, at the same times each day (Esbriet SmPC 2015; US FDA 2015).

Refer to pirfenidone Investigator's Brochure or local prescribing information for pirfenidone for details on nonclinical and clinical studies.

1.3 TRIAL RATIONALE AND BENEFIT-RISK ASSESSMENT

No approved treatments are available for the 15% of patients with ILD who have unclassifiable disease. Rather, therapeutic management is based on the most probable diagnosis after multidisciplinary discussions and consideration of the expected disease behavior (Antoniou et al. 2014). The data for pirfenidone in IPF are sufficiently encouraging (Section 1.2) to hypothesize that a beneficial clinical effect would also be observed with this agent in patients with unclassifiable fibrosing ILD.

There are several key areas for uncertainty in the assessment of the benefit-risk profile for pirfenidone in the unclassifiable ILD patient population. Fibrosing ILD might have a different natural history compared with IPF and the efficacy of pirfenidone treatment may be different in patients with unclassifiable ILD compared with patients with IPF.

MMF may have an effect on the disease course of patients with unclassifiable ILD, in particular patients with interstitial pneumonia with autoimmune features (IPAF). Patients may be receiving treatment with MMF as a concomitant therapy at the start of the trial and therefore the patient population in this trial will be stratified according to use of MMF (MMF treatment includes mycophenolate mofetil/sodium or mycophenolic acid). Patients receiving MMF concomitant therapy at the start of the trial are allowed to continue with this treatment throughout the study including the 24-week double-blind and 12-month safety follow-up periods. A similar approach had been used previously in a study of the safety and tolerability of pirfenidone in patients with systemic sclerosis−related ILD (SSc-ILD; an open-Label, randOmized, Phase 2 sTUdy of the safety and tolerability of pirfenidone when administered to patients with Systemic Sclerosis−related interstitial lung disease [LOTUSS]) (Khanna et al. 2016). The results of this trial also include data concerning the use of MMF as concomitant treatment with pirfenidone. The conclusion from this trial was that MMF, which was taken concomitantly with pirfenidone by 63.5% of patients, did not appear to affect the tolerability of pirfenidone and no particular safety concerns were noted following the combined use of MMF and pirfenidone.

2. OBJECTIVES AND ENDPOINTS

This trial will evaluate the efficacy and safety of pirfenidone in patients with fibrosing ILD who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by MDT review ("unclassifiable" ILD). Specific objectives and corresponding endpoints for the trial are outlined below (Table 1).

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of pirfenidone vs. placebo on lung function parameters	• Rate of decline in FVC measured in mL by daily handheld spirometer over the 24-week double-blind treatment period
Secondary Efficacy Objective:	
• To evaluate the efficacy of pirfenidone vs. placebo from baseline (Day 1) until Week 24 on other functional parameters, outcomes, and PROs	• Change in percent predicted FVC and in mL measured by spirometry during clinic visits • Categorical change in FVC of >5% (absolute change in percent predicted and relative change in mL), measured both by daily spirometry as well as by spirometry during clinic visits • Categorical change in FVC of >10% (absolute change in percent predicted and relative change in mL), measured both by daily spirometry as well as by spirometry during clinic visits • Change in percent predicted DLco • Change in 6MWD in meters • Change in UCSD-SOBQ score • Change in score in Leicester Cough Questionnaire • Change in cough visual analog scale • Change in total and sub-scores of the SGRQ • Non-elective hospitalization, both respiratory and all cause • Incidence of, and time to first, investigator-reported acute exacerbations (analogous to the methods described by Collard et al. 2016) • PFS, defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC (measured during a clinic visit), a >50 m decline of 6MWD, or death • PFS, alternatively defined as the time to the first occurrence of a >10% relative decline in FVC (measured during a clinic visit), non-elective respiratory hospitalization, or death • Time to death from any cause • Time to death from respiratory diseases

Objectives	Corresponding Endpoints
Safety Objective:	
• To evaluate the safety of pirfenidone vs. placebo	• Nature, frequency, severity, and timing of treatment-emergent adverse events • Dose reductions and treatment interruptions • Clinical laboratory test results • 12-lead ECGs • Withdrawals from trial treatment or trial discontinuations
Exploratory Objectives:	
• To evaluate the role of MMF treatment in ILD	• Efficacy and safety data from subgroups of patients who did or did not receive MMF treatment
• To evaluate potential biomarkers associated with fibrosis and ILD	• Biomarker data from plasma, serum, and whole blood RNA and DNA samples

6MWD=6-minute walk distance; DLco=diffusing capacity of the lung for carbon monoxide; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FVC=forced vital capacity; ILD=interstitial lung disease; MMF=mycophenolate mofetil/sodium or mycophenolic acid; PFS=progression-free survival; PRO=patient-reported outcome; RNA=ribonucleic acid; SGRQ=St. George's Respiratory Questionnaire; SOBQ=Shortness of Breath Questionnaire; UCSD=University of California, San Diego

3. TRIAL DESIGN

3.1 DESCRIPTION OF THE TRIAL

This is a multicenter, international, double-blind, two-arm, randomized, placebo-controlled Phase II trial in patients with fibrosing ILD who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by MDT review ("unclassifiable ILD"). Patients will be randomized in a 1:1 ratio, on a double-blind basis using a stratified algorithm, to receive either pirfenidone (801 mg TID) or placebo. The randomized patients will be stratified by concomitant MMF treatment (yes/no), the presence/absence of IPAF as defined by the MDT.

Most established MDTs have access to clinical, radiologic, and pathology expertise, and should have a sufficient case load of ILDs per year. Access to rheumatology expertise will be at the discretion of the MDT.

In total, approximately 90 clinical centers (sites) in Australia, Europe, the Middle East, and North America are expected to enroll approximately 250 patients. Patients who are withdrawn from the trial will not be replaced. The trial design is represented in Figure 1 .

After discussing the risks and benefits of the trial with the investigator and providing informed consent, patients will be required to taper and/or discontinue all prohibited medications (Section 4.4.2) in the 28 days prior to the start of screening during the

washout period. If a prohibited medication must be tapered, the process must start early enough so that the patient discontinues the medication in the 28 days prior to the start of screening. After completing the washout period, patients will enter screening, which lasts up to 21 days. During screening, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. Patients not taking a prohibited medication will forgo the washout period and directly enter screening.

At the end of screening, patients will be randomized (Day 1) to receive either pirfenidone or placebo (1:1 ratio).

Following treatment initiation, the daily dosage will be titrated to the full dosage of nine capsules per day over a 14-day period as outlined in Table 2 . After the titration period, trial treatment will continue through Week 24 and monitoring will be conducted by site visits. Patients should remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced or dosing is interrupted to manage an adverse event (see Section 5.1.1). Any patient with an actual or anticipated interruption of trial treatment for a period of ≥28 consecutive days will be reported by telephone to Roche‘s medical monitor or designee to discuss the circumstances of the case. Once the patient restarts trial treatment, the dose must be re-titrated over 14 days as described in Table 2 . A Follow-up Visit will occur 28 days after the end of the 24-week double-blind treatment period.

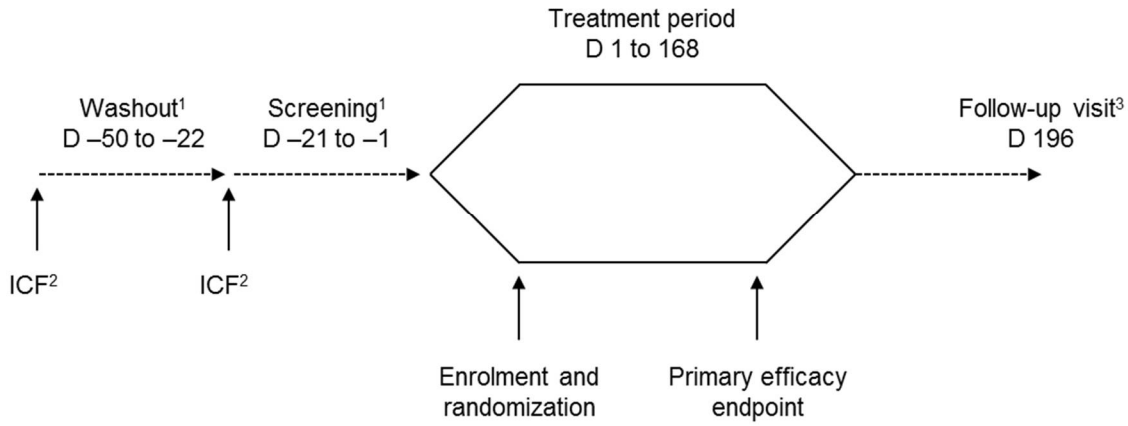
After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the safety follow-up period, the patients should be evaluated by the investigator approximately every 3 months. A final Follow-up Visit will be performed at the end of the safety period, 28 days after the last open-label dose.

Table 2 Titration Schedule

Treatment Days	Dosage
Days 1 through 7	One capsule three times daily with meals
Days 8 through 14	Two capsules three times daily with meals
Day 15 onwards	Three capsules three times daily with meals

The Sponsor will provide trial treatment on a double-blind basis. The design that will be utilized in this trial is shown in Figure 1 .

Figure 1 Trial Schema



[1] Patients will be required to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period. Patients not taking a prohibited medication will forgo the washout period and directly enter screening.

[2] Informed consent must be documented before any trial-specific screening procedure is performed, and may be obtained either at the Washout or Screening Visits.

[3] After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. A final Follow-up Visit will be performed at the end of the safety period, 28 days after the last open-label dose.

D=Day; ICF=informed consent form

The primary objective of this trial is to evaluate the efficacy of pirfenidone vs. placebo on lung function parameters by examining the rate of decline in FVC (measured in mL). A handheld spirometry device will be used by the patient to measure daily FVC at home. Confirmatory site (trial center) based FVC measurements will be conducted every 4 weeks (see Schedule of Assessments; Appendix 1). Blood samples will be obtained from patients in order to analyze clinical laboratory values and biomarkers.

The secondary objective for this trial is to evaluate the efficacy of pirfenidone vs. placebo on other functional parameters, outcomes, and patient-reported outcomes (PROs). Part of this objective will involve measuring the changes in FVC and comparing the results with baseline findings. In addition, the changes from baseline to the end of the 24-week double-blind treatment period will be investigated for several parameters, including percent predicted diffusing capacity of the lung for carbon monoxide (DLco), 6-minute walk distance (6MWD), University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ) score, Leicester Cough Questionnaire, cough visual analog scale, and total and sub-scores of the St. George's Respiratory Questionnaire (SGRQ; see Appendix 2 and the Study Manual for further information). All of these assessments will be conducted at baseline, Week 12, Week 24, and at the Early Treatment Discontinuation Visit (see Schedule of Assessments; Appendix 1). PFS will also be evaluated as part of this trial, which is defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC (measured during a clinic visit), a >50 m decline of 6MWD, or death. An alternative definition of PFS, that is the time to

the first occurrence of a >10% relative decline in FVC (measured during a clinic visit), non-elective respiratory hospitalization, or death, will also be evaluated. Further analyses will investigate the incidences of non-elective respiratory and all cause hospitalization, time to death from any cause, and time to death from respiratory diseases.

The safety objective for this trial involves evaluating the safety of pirfenidone in comparison with placebo. In order to achieve this objective, the nature, frequency, severity, and timing of treatment-emergent adverse events will be documented. Dose reductions and treatment interruptions and withdrawals from trial treatment or trial discontinuations will also be evaluated. Clinical laboratory assessments and electrocardiograms (ECGs) will be collected as per the Schedule of Assessments (Appendix 1).

The exploratory objectives for this trial are to evaluate the role of MMF treatment in ILD and to investigate potential biomarkers associated with fibrosis and ILD. To achieve the MMF objective, patients will be stratified according to whether they received treatment with MMF. The efficacy and safety data will be analyzed according to this stratification. For the biomarker objective, an investigation will be conducted with the aim of determining the impact of pirfenidone on exploratory inflammatory and fibrotic biomarkers. Transcriptomic and proteomic profiling of markers associated with the molecular pathways and cellular processes of lung injury and fibrosis will be measured.

An independent Data Monitoring Committee (iDMC) will review safety data and advise on trial conduct at least three times during the trial. A first meeting is planned 6 months after start of recruitment, and subsequently at 12 and 18 months. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted. The iDMC will be an independent body who will recommend to continue, modify or stop the trial at each meeting. The procedures that will be used by the iDMC will be detailed in an iDMC charter.

3.2 END OF TRIAL AND LENGTH OF TRIAL

After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. The end of the clinical trial is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point which is required for the statistical analysis is received, whichever is the later date. For this trial, LPLV will occur when the last patient has completed the final safety Follow-up Visit, 28 days after the final open-label dose, or when the last data point is collected in the safety follow-period.

For each patient the total length of the trial is expected to be up to a maximum of 91 weeks. The trial duration includes the washout period of up to 4 weeks, the screening period of up to 3 weeks, the double-blind treatment period of 24 weeks, the follow-up

period of 4 weeks, the open-label safety follow-up period up to 12 months (52 weeks) and a final safety Follow-up Visit 4 weeks after the last dose.

3.3 RATIONALE FOR TRIAL DESIGN

3.3.1 Rationale for Pirfenidone Dose and Schedule

In this trial, pirfenidone will be administered at a daily dose of 2403 mg. This dose will be administered orally in the form of three 267 mg capsules (801 mg) TID with food, at the same times each day. This dosing schedule is the same as the clinically recommended daily maintenance dose for patients with IPF (Esbriet SmPC 2015; US FDA 2015).

For each patient, the double-blind trial treatment period will last 24 weeks. Previous clinical studies have demonstrated that clinically significant differences in mean FVC changes from baseline have been observed in pirfenidone-treated compared with placebo-treated patients over this time frame (Noble et al. 2011). It is therefore assumed that this treatment period will be sufficient to observe any statistically significant differences in the primary endpoint. Moreover, recent data suggest that daily FVC measurements may be more sensitive to detect significant declines in lung function (Russell et al. 2016). The enrolled patients are therefore required to conduct daily spirometry assessments.

3.3.2 Rationale for Patient Population

No approved treatments are currently available to treat patients with ILD who have unclassifiable disease. Therefore, there is an unmet need to develop effective and well tolerated therapies for the treatment of patients with ILD.

Patients will be assigned to the category “unclassifiable ILD” if the participating investigator’s MDT cannot assign a case of fibrosing ILD with moderate or high confidence to any category of fibrosing ILD. As patients who fulfil the proposed research classification criteria for IPAF do not have CTD-ILD or other defined form of ILD, they will also be included within the unclassifiable ILD category. The MDT will use the available clinical, radiologic, or pathological evidence (with the involvement of rheumatology expertise at the discretion of the MDT team) to attempt to diagnose the patient with a category of fibrosing ILD (e.g., IPF, CTD-ILD, NSIP, cHP, or ILDs caused by occupational exposure or drugs). In the absence of a surgical lung biopsy or transbronchial lung cryobiopsy, the investigator must state the reason a biopsy was not performed. The available clinical, radiologic, or pathologic evidence used by the MDT will be documented in the electronic Case Report Form (eCRF). In this context, the levels of confidence are defined as follows:

- High confidence: a specific diagnosis is highly likely (i.e., usual interstitial pneumonia [UIP] pattern on high-resolution computed tomography [HRCT] in the case of IPF)
- Moderate confidence: the MDT arrives at a “working diagnosis” of a particular ILD which is sufficient to lead to a specific therapeutic strategy (i.e. antifibrotic therapy in the case of IPF, immunosuppressive therapy in the case of CTD-ILD)

- Low confidence: the MDT may have a suspicion of a particular ILD but considers the available evidence insufficient to inform therapeutic strategy.

The following, non-exhaustive, list of patient populations will therefore be eligible for enrollment:

- Patients with “unclassifiable ILD”
- Patients fulfilling research classification criteria for IPAF (Fischer et al. 2015)
- Patients with a low confidence diagnosis of NSIP, cHP, CTD-ILD, etc.

Patients diagnosed with any fibrosing or non-fibrosing ILD with high or moderate confidence will be excluded from the trial. Patients with IPF, irrespective of the level of confidence of diagnosis, cannot be included in the trial.

3.3.3 Rationale for Control Group

No approved treatments are available for the patients with ILD who have unclassifiable disease, and no controlled clinical trials have been performed to date in this patient population. In the absence of any clinically recognized comparator, patients in the control group will receive placebo treatment during the 24-week double-blind treatment period.

3.3.4 Rationale for Concomitant MMF Therapy

In this trial, patients may be receiving concomitant therapy with MMF (MMF treatment includes mycophenolate mofetil/sodium or mycophenolic acid) when the trial starts. As MMF may have an effect on the disease course of unclassifiable ILD, patients will be stratified according to whether they received concomitant MMF treatment during the trial (see Section 3.1). In the LOTUSS trial, which included patients with SSc-ILD, all patients who were enrolled on the basis of a stable dose of allowable SSc medication, could receive treatment with MMF. In this trial, the maximum allowed dose of MMF was 1.5g two times daily (BID), but the dosage was otherwise left to the discretion of the investigator. For the current trial, a similar treatment approach will be used. MMF will be used at a stable dose of up to 1.5g (or equivalent) BID that should be kept constant unless safety considerations require dose reduction, dose interruption, or stopping MMF altogether. Patients enrolled without MMF treatment should not start MMF during the blinded treatment period.

MMF was chosen as the permitted concomitant therapy as it is a potential treatment choice in patients who have secondary interstitial lung fibrosis related to autoimmune disease (Chartrand et al. 2016, Fischer et al. 2013, Khanna et al. 2016, Volkman et al. 2016). In addition, MMF is used in patients with autoimmune fibrosis of an unknown etiology.

Recruitment into the trial would be limited, if concomitant MMF treatment was not permitted for patients who are receiving therapeutic benefit from this treatment. Allowing

MMF as concomitant therapy also enables the clinical community to gather further information on the safety of MMF in this patient population.

3.3.5 Rationale for Biomarker Assessments

Certain biomarkers may be differentially expressed in patients with unclassifiable ILD and may change as a result of pirfenidone treatment (e.g., possibly cytokines, chemokines, and other cellular and molecular markers of lung injury and fibrosis). The blood biomarker samples that are being obtained for this trial may help identify the serum and plasma proteins or blood ribonucleic acid (RNA) biomarkers related to disease progression and/or may be used to assess their response to pirfenidone therapy.

Transcriptomic and protein markers associated with the molecular pathways and cellular processes of lung injury and fibrosis will be measured. This may include, but is not restricted to, measurement of CCL18, MMP7, CXCL13, and COMP.

Serum, plasma, and whole blood (for RNA analysis) samples will be acquired at baseline, Week 4, Week 12, Week 24, and at the Early Treatment Discontinuation Visit (see the Schedule of Assessments; Appendix 1).

Optional Research Biosample Repository (RBR) whole blood samples for deoxyribonucleic acid (DNA) extraction, described in Section 4.5.8 of the protocol, will also be collected at baseline to examine genetic polymorphisms and their potential role in the pathogenesis and associated clinical outcomes of unclassifiable ILD. Patient participation for this assessment is voluntary and declining participation to collect biomarker data will not influence eligibility for this trial.

3.3.6 Rationale for Disease Response–based Endpoints

The primary objective of this trial is to evaluate the efficacy of pirfenidone vs. placebo on lung function parameters by examining the rate of decline in FVC measured in mL. FVC will be measured daily using a handheld spirometer by the patient and every 4 weeks at the site (see Schedule of Assessments; Appendix 1) during the 24-week double-blind treatment period. Changes in FVC have been examined in several different clinical studies which enrolled patients with unclassifiable ILD (Leung et al. 2015; Ryerson et al. 2013; Solomon et al. 2013), and are generally accepted as a valid measure of disease course in patients with ILD.

Other disease response-based parameters that will be examined in this trial include predicted DLco, 6MWD, UCSD-SOBQ, Leicester Cough Questionnaire, cough visual analog scale, and total and subscores of the SGRQ (see Appendix 2). All of these parameters have been used extensively as disease response-based parameters in studies involving similar patient populations (Jones et al. 2011; Key et al. 2010; Ryerson et al. 2014; Swigris et al. 2010, 2012).

3.3.7 Rationale for PRO Assessments

Several PRO assessments will be conducted in this trial, including the UCSD-SOBQ, the Leicester Cough Questionnaire, the cough visual analog scale, and the SGRQ (see Appendix 2 and the Study Manual for further information). All of these assessments have been used extensively as PRO measures in studies involving similar patient populations (Jones et al. 2011; Key et al. 2010; Ryerson et al. 2014; Swigris et al. 2010, 2012). No bias is assumed in the results of these assessments.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 250 patients with unclassifiable fibrosing ILD will be enrolled in this trial.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for trial entry:

1. Signed Informed Consent Form
2. Age ≥18–85 years
3. Able to comply with the trial protocol, according to the investigator's judgment
4. Confirmed fibrosing ILD which, following MDT review, cannot be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD (e.g. chronic hypersensitivity or connective tissue disease-ILD [CTD-ILD])
5. Progressive disease as considered by the investigator using the following definition:
    a. Patient deterioration within the last 6 months, which is defined as:
        i. A rate of decline in FVC >5% OR
        ii. Significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes.
6. Extent of fibrosis >10% on high-resolution computed tomography (HRCT; visual scoring) within the last 12 months
7. FVC ≥45% of predicted value
8. Diffusing capacity of the lung for carbon monoxide (DLco) ≥30% of predicted value
9. Forced expiratory volume in 1 second (FEV_1)/FVC ratio ≥0.7
10. 6-minute walk distance (6MWD) ≥150 meters
11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1% per year during the treatment period and for at least58 days after the last dose of trial treatment:
    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, hormonal contraceptives including those 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.

For men: 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 trial treatment. Men must refrain from donating sperm during this same period

b. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 118 days after the last dose of trial treatment to avoid exposing the embryo

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.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

1. Diagnosis with moderate or high confidence of nonspecific interstitial pneumonia (NSIP) and any ILD with an identifiable cause such as CTD-ILD, chronic hypersensitivity pneumonitis (cHP), or others
2. Diagnosis of idiopathic pulmonary fibrosis (IPF) independent of the confidence level
3. History of unstable angina or myocardial infarction during the previous 6 months
4. Pregnant or lactating, or intending to become pregnant during the trial
5. A positive urine pregnancy test, which was confirmed with a positive serum pregnancy test. Women with a confirmed pregnancy will be excluded from trial participation and must discontinue trial treatment
6. Treatment with high dose systemic corticosteroids (i.e., >15 mg/d of prednisolone or equivalent), or any immunosuppressant other than MMF, at least 4 weeks prior to screening. Patients being treated with MMF should be on a stable dose that is

expected to remain stable throughout the trial and was started at least 3 months prior to screening

7. Patients previously treated with pirfenidone or nintedanib
8. Patients treated with N-acetyl-cysteine (NAC) for fibrotic lung disease, at any time within the 4 weeks of the screening period
9. Drug treatment for any type of pulmonary hypertension (e.g. sildenafil, endothelin receptor antagonist [ERA], etc.)
10. Participation in a trial of an investigational medicinal product within the last 4 weeks
11. Significant co-existent emphysema (extent greater than extent of fibrosis on HRCT within the last 12 months)
12. Significant other organ co-morbidity including hepatic or renal impairment
13. Previous intolerance or allergy to the trial treatment
14. Pregnant patients, or women of child-bearing potential, not using a reliable contraceptive method
15. Unable to provide informed written consent
16. Predicted life expectancy <12 months or on an active transplant waiting list
17. Use of any tobacco product in the 12 weeks prior to the start of screening, or any unwillingness to abstain from their use through to the Follow-up Visit
18. Illicit drug or alcohol abuse within 12 months prior to screening, according to the investigator's judgment
19. Planned major surgery during the trial
20. Hypersensitivity to the active substance or to any of the excipients of pirfenidone
21. History of angioedema
22. Concomitant use of fluvoxamine
23. Clinical evidence of any active infection which according to the investigator's judgment may interfere with trial conduct, measurement of pulmonary function, or impact the course of the ILD
24. Any history of hepatic impairment, elevation of transaminase enzymes, or the confirmation of any of the following liver function test (LFT) criteria above the specified limits:
    a. Total bilirubin above the upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × ULN
    c. Alkaline phosphatase >2.0 × ULN.
25. Creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault formula
26. Any serious medical condition, clinically significant abnormality on an ECG at screening, or laboratory test results (hematology, serum chemistry, and urinalysis)

that, in the opinion of the investigator, may pose an additional risk to the patient following the administration of trial treatment

27. An ECG with a heart rate corrected QT interval (corrected using Fridericia's formula [QTcF]) ≥500 ms at screening, or a family or personal history of long QT syndrome.

Re-screening may be considered for patients who do not show sufficient disease deterioration in accordance to the protocol at the time of the initial screening. Re-screening is permitted if there is strong evidence of clinical worsening based on the Investigator's judgement and only upon receipt of official approval from the Study Management Team. In such cases, re-screening may be performed after a minimum of 4-weeks lapse from the initial screening date.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized 1:1 to receive either pirfenidone versus placebo. The randomization process will be conducted using a validated interactive voice or web-based response system (IxRS). To guard against systematic selection bias and ensure comparability of treatment groups, the randomization will be stratified by concomitant MMF treatment (yes/no), the presence/absence of IPAF as defined by the MDT.

To maintain the double-blind nature of the trial, the pirfenidone and placebo treatments will be identical in appearance (see Section 4.3.1.1).

The investigational site personnel and the patients will be blinded to treatment assignment following randomization. The iDMC and any personnel performing any interim analysis (as applicable) will be unblinded to the treatment throughout the trial.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

Unblinding should not necessarily result in the withdrawal of a patient from the trial. After unblinding, the patient will be withdrawn from the 24-week double-blind treatment period. If the unblinding was based on the investigator's safety concerns and reveals that the patient had been treated with pirfenidone, the patient will be withdrawn from the trial. In this case, the patient will attend the Early Treatment Discontinuation Visit and thus end his/her participation in the trial. However, if unblinding reveals that the patient had not been treated with pirfenidone and that the investigator has no further safety concerns, then the patient may be offered the option to continue into the 12-month open-label pirfenidone safety follow-up period. In this case, the patient will attend the Early Treatment Discontinuation Visit (± 28 days after the last dose of the double-blind

treatment) and on the same day begin his/her participation in the 12-month open-label pirfenidone safety follow-up period.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to trial treatment.

4.3 TRIAL TREATMENT

The investigational medicinal product (IMP) for this trial is pirfenidone.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Pirfenidone and Placebo

Pirfenidone and placebo will be supplied by the Sponsor as 267 mg capsules in a bottle. For information on the formulation and handling of pirfenidone, see the Investigator's Brochure or local prescribing information for pirfenidone.

The chemical name of pirfenidone is 5-methyl-1-phenyl-2-1(H)-pyridone.

Pirfenidone (pirfenidone 267 mg) will be supplied as white, hard gelatin capsules.

Each pirfenidone capsule contains 267 mg of pirfenidone, and the following inactive ingredients:

- Capsule content: microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate
- Capsule shell: gelatin and titanium dioxide.

Pirfenidone should be stored according to the IMP label and the bottle should be tightly closed.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Pirfenidone and Placebo

In this trial, pirfenidone will be administered at a daily dose of 2403 mg. This dose will be administered orally in the form of three 267 mg capsules (801 mg) TID with food, at the same times each day.

Patients will initially take one capsule TID with meals. Following treatment initiation, the daily dosage will be titrated to the full dosage of nine capsules per day over a 14-day period as outlined in Table 2 . Temporary dosage reduction, treatment interruption, or discontinuation should be considered in order to effectively manage any treatment-emergent adverse reactions. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.

Any overdose or incorrect administration of trial treatment should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of trial treatment should be recorded on the Adverse Event eCRF. Section 5.3.5.11 summarizes available safety data related to overdosing of pirfenidone.

Placebo will be supplied by the Sponsor in the form of capsules with identical appearance and size as the pirfenidone capsule. The placebo capsules will contain microcrystalline cellulose.

Patients will be asked to take the IMP according to site instructions. IMP accountability will be performed at the next site visit.

4.3.2.2 Dose Modification/Restarting Treatment

Patients should remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced or dosing is interrupted to manage an adverse event (see Section 5.1.1). Any patient with an actual or anticipated interruption of trial treatment for a period of ≥ 28 consecutive days will be reported by telephone to Roche‘s medical monitor or designee to discuss the circumstances of the case. Once the patient restarts trial treatment, the dose must be re-titrated over 14 days as described in Table 2

.

4.3.3 Investigational Medicinal Product Accountability

The IMP required for completion of this trial (pirfenidone) will be provided by the Sponsor. The trial site will acknowledge receipt of IMPs, using the IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the trial site according to the trial site’s institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of the IMP received at, dispensed from, returned to, and disposed of by the trial site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Pirfenidone

After completion of the double-blind treatment period, the Sponsor will offer the possibility to the patients to receive continued access to pirfenidone in a safety follow-up period of up to 12 months, within this clinical trial protocol. A final Follow-up Visit will be performed at the end of the safety period, 28 days after the last open-label dose.

At the end of the 24-week double-blind treatment period, in order to maintain blinding, all patients will discontinue treatment over a 28-day period and return for the Follow-up Visit.

For patients who could benefit from participating in the 12-month safety follow-up period, according to the investigator's judgment, open-label pirfenidone will be started on the 28-day Follow-up Visit, using the titration schedule in Table 2 . During the 12-month safety follow-up period, initially, patients will be evaluated at monthly visits for the first 6 months. At the end of the first 6 months, patients will be evaluated at each site visit occurring approximately every 3 months until the end of the safety follow-up period. In addition, at the end of the first 6 months, patients will perform home pregnancy tests at each month where there is no site visit. Patients will be provided with home pregnancy test kits and will be instructed to contact the site immediately should the test result be positive. In such cases, the patient must visit the site for a confirmatory serum pregnancy test. Refer to Schedule of Assessments for the assessments to be performed during this safety follow-up period (Appendix 1). The dose of pirfenidone used during the safety follow-up period is in accordance to section 4.3.2.1.

Following the end of the 12-month safety follow-up period, the Sponsor will offer post-trial access to the trial treatment (pirfenidone), free of charge, to eligible patients in accordance with the Roche Global Policy on Continued Access to IMP, as outlined below.

A patient will be eligible to receive Pirfenidone (Esbriet®) after completing the trial if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued trial treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Pirfenidone (Esbriet®) after completing the trial if any of the following conditions are met:

- Pirfenidone (Esbriet®) is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of Pirfenidone (Esbriet®)or data suggest that Pirfenidone (Esbriet®)is not effective for unclassifiable ILD
- The Sponsor has safety concerns regarding Pirfenidone (Esbriet®)as treatment for unclassifiable ILD
- Provision of Pirfenidone (Esbriet®)is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to IMP is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from the washout period until 28 days after the last dose of trial treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All protocol-allowed medications taken by the patient for concomitant disease(s) should be continued as necessary during the trial and be recorded on the eCRF. Treatments prescribed to patients should be adapted according to the local standard of care practice.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the trial and should be tapered and/or discontinued in the 28 days prior to screening:

- Investigational therapy other than trial treatment
- High dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for longer than 28 days
- Immunosuppressive therapies (e.g. azathioprine)
- Treatment with NAC for fibrotic lung disease, at any time within the 4 weeks of the screening period; intermittent use of NAC for other conditions is permitted
- Fluvoxamine and other cytochrome P450 1A2 (CYP1A2) inhibitors
- CYP1A2 inducers.

If down titration of prohibited therapy is required, it must be done during the 28-day washout period.

4.4.2.1 Corticosteroids

Pirfenidone should not be used in combination with high-dose corticosteroids (>15 mg/day) for periods longer than 28 days. Co-administration of pirfenidone with lower doses of corticosteroids is at the discretion of the investigator.

4.4.2.2 Fluvoxamine and Other CYP1A2 Inhibitors

In a Phase I study, the co-administration of pirfenidone and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes [CYP2C9, 2C19, and 2D6]) resulted in a 4-fold increase in exposure to pirfenidone in non-smokers (Esbriet SmPC 2015). Pirfenidone is therefore contraindicated in patients who are receiving concomitant fluvoxamine. Fluvoxamine treatment should be discontinued prior to the initiation of pirfenidone therapy and avoided during therapy due to the reduced clearance of pirfenidone. Other therapies that are inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. CYP2C9, 2C19, and 2D6) should be avoided during pirfenidone treatment.

In vitro and *in vivo* extrapolations have indicated that strong and selective inhibitors of CYP1A2 (e.g. enoxacin) have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold (Esbriet SmPC 2015). If concomitant use of pirfenidone with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of pirfenidone should be reduced to 801 mg daily (one capsule TID).

Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate inhibitor of CYP1A2) increased the exposure to pirfenidone by 81% (Esbriet SmPC 2015). If ciprofloxacin at a dose of 750 mg BID cannot be avoided, the dose of pirfenidone should be reduced to 1602 mg daily (two capsules TID). Pirfenidone should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily. Pirfenidone should also be used with caution in patients treated with other moderate inhibitors of CYP1A2 (e.g. amiodarone, propafenone).

Caution should be exercised if CYP1A2 inhibitors are being used concomitantly with pirfenidone and potent inhibitors of one or more of the other CYP isoenzymes involved in the metabolism of pirfenidone (Esbriet SmPC 2015). These isoenzymes include CYP2C9 (inhibitors include amiodarone and fluconazole), CYP2C19 (inhibitors include chloramphenicol), and CYP2D6 (inhibitors include fluoxetine and paroxetine).

4.4.2.3 CYP1A2 Inducers

Concomitant use of strong inducers of CYP1A2 should be avoided during pirfenidone therapy following the results of a Phase I interaction study that found that pirfenidone exposure was 50% lower in smokers compared with non-smokers (Esbriet SmPC 2015). Smoking induces the CYP1A2 isoenzyme. Patients should therefore be encouraged to discontinue the use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone.

In the case of moderate inducers of CYP1A2 (e.g. omeprazole), concomitant use may theoretically result in a lowering of pirfenidone plasma levels (Esbriet SmPC 2015).

Co-administration of pirfenidone with medicinal products that act as potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of pirfenidone (e.g., rifampicin) may result in significant lowering of pirfenidone plasma levels (Esbriet SmPC 2015). These medicinal products should therefore be avoided whenever possible.

4.4.2.4 Other Medications

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication strongly inhibits or induces CYP1A2. In addition, the investigator should contact the Medical Monitor if questions arise regarding specific medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.4.3 Prohibited Food

The consumption of grapefruit juice will be prohibited from the start of screening through to the Follow-up visit.

4.4.4 Additional Restrictions

The use of any tobacco product will be prohibited from 12 weeks prior to the start of screening through to the Follow-up Visit.

4.5 TRIAL ASSESSMENTS

Please see Appendix 1 for the Schedule of Assessments to be performed during the trial.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the trial must be obtained before performing any trial-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the trial site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant respiratory diseases (asthma, chronic obstructive pulmonary disease, and pneumonia), reproductive status, smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from the washout period until 28 days after the last dose of trial treatment will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination will be performed at screening and will include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed (see the Schedule of Assessments; Appendix 1). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. All vital sign measurements are to be obtained prior to any blood draws scheduled at the same time.

4.5.5 FVC

FVC is defined as the maximal volume of gas that can be exhaled following full inhalation by exhaling as forcefully and rapidly as possible. FVC has been an established measure of pulmonary function in patients with IPF for many decades (du Bois et al. 2011). Longitudinal changes in serial measures of lung volume are a widely accepted reflection of disease progression in patients with IPF and a commonly used primary endpoint in therapeutic studies.

If a patient is routinely treated with a short-acting bronchodilator (for example albuterol, salbutamol), the bronchodilator should be taken approximately 30 minutes prior to the on-site spirometry.

4.5.6 Handheld Spirometry

Patients will perform a single spirometry reading at approximately the same time each day. For this purpose, trial participants will be provided with a portable handheld Micro spirometer ([redacted], England). The Micro spirometer measures FEV_1 and FVC by means of a turbine volume transducer and provides a digital read out registered in liters at body temperature and pressure saturated with water vapor (BTPS). Each spirometer will be factory calibrated. Patients will be given 60 minutes dedicated instruction on how to undertake spirometry at the Screening Visit. Patients will be asked to use the device during the screening period and will be subsequently retrained at the Baseline Visit. Additional refresher training will be provided after 1 month.

As the primary endpoint of this trial is to determine the rate of decline in FVC measured by daily handheld spirometer, further support to effectively use this device will be provided to the patients. The Sponsor will select a healthcare company that will be responsible for providing home nursing services for the participating sites. The vendor is responsible for ensuring that all home nursing professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed.

Sites will communicate directly with the vendor in their country when patients have entered the trial. The trained nursing professional will conduct the visit at the patient's home or at another suitable location in order to provide handling evaluations and quality assurance for the daily spirometer assessments. The expected number of home visits is stated in the Schedule of Assessments (Appendix 1).

4.5.7 Other Trial Assessments

Further information on the other assessments (e.g., FVC, DLco, 6MWD, UCSD-SOBQ, Leicester Cough Questionnaire, cough visual analog scale, and SGRQ) that will be conducted as part of this trial can be found in Appendix 2 and the Study Manual.

4.5.8 Laboratory and Biomarker Samples

All of the laboratory tests will be conducted by the trial site's local laboratory. Biomarker samples will first be sent to a central laboratory and then to outsourced contract research organizations (CROs) or the Sponsor for testing.

The following laboratory and biomarker samples will be collected:

- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, lactate dehydrogenase (LDH)
- Pregnancy test:
- All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Blood samples for exploratory research on biomarkers (see Appendix 1).

Exploratory biomarker research may include, but will not be limited to CCL18, MMP7, CXCL13, and COMP.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Whole blood, plasma, and serum samples collected for biomarker analyses will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the trial, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified time points, as outlined in the Schedule of Assessments (see Appendix 1), and may be obtained at unscheduled time points as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs, when possible, should be obtained prior to other procedures scheduled at the same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent trial file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and the QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory. Refer to section 5.1.1.8 for details on protocol management of increases in QT interval.

4.5.10 Patient-Reported Outcomes

Several PRO assessments will be conducted in this trial, including the UCSD-SOBQ, the Leicester Cough Questionnaire, the cough visual analog scale, and the SGRQ (see Appendix 2). The impact of potential bias on these outcomes will not be investigated.

PRO data will be collected via questionnaires to document the treatment effect and to evaluate the benefit of pirfenidone. The questionnaires, translated into the local language as required, will be completed in their entirety at specified time points during the trial (see Appendix 1). To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient

receives any information on disease status and prior to the performance of non-PRO assessments, unless otherwise specified.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be collected for research purposes, including, but not limited to, research on biomarkers related to pirfenidone or unclassifiable ILD:

- Leftover plasma, serum, and whole blood RNA (*PAX* gene) samples
- RBR whole blood for DNA extraction

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this trial, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this trial but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to trial investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on trial data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Patient Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from this trial does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this trial.

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, TRIAL, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the trial at any time for any reason. In addition, the investigator has the right to withdraw a patient from the trial at any time. Reasons for withdrawal from the trial may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the trial
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as non-adherence with the dosing regimen, including the dose-titration guidance for starting trial treatment
- Lung transplantation

Patients who undergo lung transplantation during the trial will be discontinued at the time of hospitalization for transplantation.

Every effort should be made to obtain information on patients who withdraw from the trial. The primary reason for withdrawal from the trial should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the trial will not be replaced.

4.6.2 Trial Treatment Discontinuation

Patients must discontinue trial treatment if they experience any of the following:

- Pregnancy
- Hepatic or renal impairment
- LFT elevations that require discontinuation
- Angioedema

The primary reason for early trial treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue trial treatment prematurely will not be replaced.

4.6.3 Trial and Site Discontinuation

The Sponsor has the right to terminate this trial at any time. Reasons for terminating the trial may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the trial.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No trial activity (i.e., all patients have completed the trial and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Pirfenidone is approved for the treatment of IPF in the US, and for the treatment of mild to moderate IPF in the EEA and Canada (Esbriet SmPC 2015; Health Canada 2016; US FDA 2015). However, the efficacy and safety of pirfenidone in patients with unclassifiable ILD has not been fully elucidated. The safety plan for patients in this trial is based on clinical experience with pirfenidone in completed and ongoing studies predominately involving patients with IPF. The anticipated important safety risks for pirfenidone are outlined below. Please refer to the pirfenidone Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the trial, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

An iDMC will review safety data and advise on trial conduct (see Section 3.1). The procedures that will be used by the iDMC will be detailed in an iDMC charter.

5.1.1 Risks Associated with Pirfenidone

Treatment with pirfenidone was consistent with the known safety profile and generally well tolerated in patients who received treatment in the clinical development program.

Almost all patients experienced an adverse event (99.0% in the pirfenidone 2403 mg/day group and 97.9% in the placebo group). The most common adverse events in the pirfenidone group were GI events (nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease [GERD], and constipation), respiratory-related events (cough, dyspnea, IPF, upper respiratory tract infection, nasopharyngitis, bronchitis, and sinusitis), fatigue, decreased weight, anorexia, back pain, arthralgia, headache, dizziness, insomnia, rash, and photosensitivity reactions.

5.1.1.1 Hepatic Function

Elevations in ALT and AST >3 × ULN have been reported in patients receiving therapy with pirfenidone. Rarely, these have been associated with concomitant elevations in bilirubin. LFTs (ALT, AST, and bilirubin) should be conducted prior to the initiation of treatment with pirfenidone and subsequently at monthly intervals for the first 6 months. In the event of significant elevation of liver aminotransferases, the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed in Table 3 . See Sections 5.4.2.11 and 6.4.1 of the Investigator's Brochure for more details.

Patients with clinically significant hepatic impairment will be excluded from this trial (see Section 4.1.2).

5.1.1.2 Gastrointestinal effects

Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, GERD, and abdominal pain have been more frequently reported in the pirfenidone treatment groups than in the placebo groups. Dose reduction or interruption for gastrointestinal events was required in 18.5% of patients in the pirfenidone 2403 mg/day group compared with 5.8% of patients in the placebo group. In addition, 2.2% of patients in the pirfenidone 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared with 1.0% of patients in the placebo group. The most common (>2%) gastrointestinal events that led to dose reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dose modifications may be necessary in some cases of gastrointestinal adverse reactions. Taking pirfenidone with food is recommended. See Sections 5.4.2.10 and 6.4.1 of the Investigator's Brochure for more details.

The incidence of gastrointestinal events was higher early in the course of pirfenidone treatment (with the highest incidence occurring during the initial 3 months) and usually decreased over time.

5.1.1.3 Photosensitivity Reaction or Rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with pirfenidone (see Investigator's Brochure for more details). Patients should be instructed to use an effective sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report any symptoms of photosensitivity reaction or rash. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash. See Sections 5.4.2.13 and 6.4.1 of the Investigator's Brochure for more details.

5.1.1.4 Angioedema

Reports of angioedema (some serious), such as swelling of the face, lips, and/or tongue which may be associated with difficulty breathing or wheezing, have been received in association with use of pirfenidone in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of pirfenidone should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. Pirfenidone should not be used in patients with a history of angioedema due to pirfenidone treatment. See Sections 5.4.2.16 and 6.4.1 of the Investigator's Brochure for more details.

5.1.1.5 Dizziness

In the pooled Phase 3 analysis (PIPF-004/006/016), dizziness was reported for a larger proportion of pirfenidone patients than placebo patients (18.0% pirfenidone vs. 11.4% placebo), and the majority of pirfenidone patients who reported dizziness first did so

during the initial 3 months of treatment (72/112, 64.3%). Two (0.3%) pirfenidone patients and one (0.2%) placebo patient had Grade 3 dizziness. There were no Grade 4 events, serious adverse events, hospitalizations, treatment discontinuations, or deaths for dizziness in either group. See Sections 5.4.2.9 and 6.4.1 of the Investigator's Brochure for more details.

An analysis of the relationship between dizziness and subsequent falls revealed that six of 112 (5.4%) pirfenidone patients who reported dizziness experienced a fall at some time after the first report of dizziness.

5.1.1.6 Fatigue

In the pooled Phase 3 analysis (PIPF-004/006/016), fatigue was reported for 26.0% of pirfenidone patients and 19.1% of placebo patients. The majority of pirfenidone patients who reported fatigue first did so during the initial 9 months of treatment (127/162, 78.4%), with 81/162 (50.0%), experiencing it within the first month. In the pirfenidone group, 1.1% of patients had a Grade 3 event; there were no Grade 4 events, serious adverse events, hospitalizations, treatment discontinuations, or deaths. In the placebo group, 0.8% of patients had a Grade 3 event, one (0.2%) patient had a serious adverse event, and one (0.2%) patient was hospitalized for fatigue; there were no Grade 4 events, deaths, or treatment discontinuations. See Section 6.4.1 of the Investigator's Brochure for more details.

5.1.1.7 Weight loss

In the pooled Phase 3 analysis (PIPF-004/006/016), the adverse event of weight decrease was reported for a larger proportion of pirfenidone patients than placebo patients (10.1% pirfenidone vs. 5.4% placebo), and the majority of pirfenidone patients who reported an adverse event of weight decrease first did so during the initial 6 months of treatment (39/63, 61.9%). In the pirfenidone group, two (0.3%) patients had Grade 3 adverse events, one (0.2%) patient had a serious adverse event, and five (0.8%) patients discontinued trial treatment for this adverse event; there were no Grade 4 events, hospitalizations, or deaths. In the placebo group, one (0.2%) patient had a serious adverse event and was hospitalized; there were no Grade 3 or 4 events, deaths, or treatment discontinuations for this adverse event. See Sections 5.4.2.14 and 6.4.1 of the Investigator's Brochure for more details.

5.1.1.8 Management of Increases in QT Interval

In the event of a QTcF interval of >500 ms or an increase from baseline of >60 ms, a repeat ECG must be obtained within 24 hours. If the QTcF finding is confirmed by the repeat ECG and verified by the site (trial center) or local cardiologist, pirfenidone treatment should be discontinued and a decision on trial treatment discontinuation should be made, as described in Section 4.6.1.. If an alternative explanation is identified (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, and

severe bradycardia) and the abnormality resolves, restarting trial treatment should be considered by the investigator in consultation with the Medical Monitor or designee. If the investigator, in consultation with the Medical Monitor or designee, considers it clinically appropriate to recommence trial treatment, treatment should be restarted as described in Table 2 .

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 3 .

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events with Pirfenidone

Event	Action to Be Taken

Elevated aminotransferase results	• For patients with a >3 to <5 × ULN increase in ALT or AST levels without hyperbilirubinemia:
	  • Discontinue confounding medications
	  • Monitor the patient closely, including repeating liver chemistry tests
	  • Maintain the full daily dose, if clinically appropriate, or reduce or interrupt the dose (e.g., until liver chemistry test results are within normal limits) with subsequent re-titration to full dose if well tolerated.
	• For patients with a >3 to <5 × ULN increase in ALT or AST levels with symptoms or hyperbilirubinemia:
	  • Discontinue pirfenidone and do not rechallenge the patient.
	• For patients with a >5 × ULN increase in ALT or AST levels:
	  • Trial treatment should be permanently discontinued.

Gastrointestinal disorders	• Dose modifications may be necessary in some cases of gastrointestinal adverse reactions. • Taking pirfenidone with food is recommended.

Photosensitivity reaction and rash	• Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with pirfenidone.
	• Instruct patients to:
	  • Wear clothing that protects against sun exposure
	  • Avoid other medicinal products that cause photosensitivity
	  • Report symptoms of photosensitivity reaction or rash.
	• Adjust dose or temporarily discontinue treatment (if necessary).
	• Use an effective sunblock on a daily basis.

Angioedema	• Immediately discontinue treatment. • Manage patients according to standard of care. • Pirfenidone should not be used in patients with a history of angioedema.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the trial.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in trial treatment or concomitant treatment or discontinuation from trial treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of trial treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
    - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to trial treatment
- Is a significant medical event according to the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this trial include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the trial treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the trial treatment is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by trial personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of trial treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of trial treatment, all adverse events will be reported until 28 days after the last dose of trial treatment (Follow-up Visit).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.
Note: based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the trial treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of trial treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of trial treatment, or reintroduction of trial treatment (as applicable)
- Known association of the event with the trial treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by

changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in trial treatment (e.g., dosage modification, treatment interruption, or early treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant according to the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in trial treatment (e.g., dosage modification, treatment interruption, or early treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant according to the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality from any cause and mortality from respiratory diseases are included as efficacy endpoints. Mortality is also included as part of the PFS efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of unclassifiable ILD should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-trial deaths, regardless of relationship to trial treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths in this trial.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the Screening Visit for this trial. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Unclassifiable ILD

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on ≥10% relative decline in FVC or a >50 m decline in 6MWD. In rare cases, the determination of clinical progression will be based on symptomatic deterioration or a decline in DLco of ≥15%. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care

- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the trial or was scheduled during the trial when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying ILD

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of trial treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of trial treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

There is limited clinical experience with regards to overdose with pirfenidone. Multiple doses of pirfenidone up to a dose of 4806 mg/day (six 267 mg capsules TID) have been administered to healthy adult volunteers over a 12-day dose escalation period. Adverse reactions were mild, transient, and consistent with the most frequently reported adverse reactions for pirfenidone.

In the event of a suspected overdose, supportive medical care should be provided including monitoring of vital signs and close observation of the clinical status of the patient.

No deaths occurred in dogs that received single oral doses of pirfenidone up to 1000 mg/kg (approximately 11 times the maximum recommended daily dose in adults on a mg/m^2 basis). Clinical signs included vomiting, weakness of limbs, hypoactivity, salivation, mydriasis, shivering, and abnormal vocalization. The maximum nonlethal dose in rats was 500 mg/kg (approximately two times the maximum recommended daily dose in adults on a mg/m^2 basis). Clinical signs in rats included decrease in locomotor activity, bradypnea, lacrimation, salivation, ptosis, mydriasis, prone position, lateral position, and hypothermia.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to trial treatment:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for all sites

Medical Monitor/Roche Medical Responsible: [redacted] (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted] (Secondary)

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information for all sites

Roche Medical Responsible: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of trial patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible individual (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible individual contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Trial Treatment Initiation

After informed consent has been obtained but prior to initiation of trial treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Trial Treatment Initiation

After initiation of trial treatment, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of trial treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur ≥ 28 days after the last dose of trial treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the trial or within 58 days after the last dose

of trial treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue trial treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the trial or within 118 days after the last dose of trial treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to trial treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to trial treatment or the female partner of a male patient exposed to trial treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Pirfenidone Accidental Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For Pirfenidone, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with Pirfenidone, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to trial treatment or trial-related procedures until a final outcome can be reported.

During the treatment period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the trial should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the last dose of trial treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior trial treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

Pirfenidone Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the trial with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the trial population at some frequency independent of trial treatment exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Cough
- Dyspnea
- Hypoxemia
- Lung crepitations

The iDMC will monitor the incidence of the above-listed anticipated events during the trial. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in the ITT population will be assigned to the treatment groups as randomized.

The safety population is defined as all treated patients (at least one drug intake of pirfenidone or placebo). Patients in the safety population will be assigned to treatment groups according to the treatment they received.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this trial is hypothesis generation regarding the efficacy of pirfenidone vs. placebo on lung function parameters on the basis of rate of decline in FVC, as measured by daily handheld spirometry.

A total sample size of approximately 250 patients is planned, and patients will be randomized in a 1:1 ratio. The randomization will be stratified by concomitant MMF treatment (yes/no), the presence/absence of IPAF as defined by the MDT.

The planned sample size is based on the statistical hypothesis of the primary endpoint and assumes 80% power and a two-sided significance level of 5% using a student’s t-test. It is assumed, after inspection of historical data, that FVC decline in the placebo arm is 85 mL with a common standard deviation of 70 mL, which can be reduced to 60 mL with a common standard deviation of 70 mL in the pirfenidone arm. In this scenario, 125 patients per treatment arm are needed to detect this treatment effect with 80% power.

These assumptions are based upon the following considerations: in IPF, the annual rate of decline of FVC is approximately 200 mL. Owing to the fact that patients with unclassifiable ILD have rates of disease progression in the range of patients with IPF,

albeit with a lower mortality rate (Ryerson et al. 2013), a similar decline rate of 200 mL/year, equivalent to a 100 mL decline over a treatment period of 24 weeks, can be expected. However, a yet unknown proportion of patients in this trial will be treated concomitantly with MMF. In a previous study of CTD-ILD (Fischer et al. 2013), MMF was found to have beneficial effects on lung functions in these patients. While CTD-ILD is a distinct entity from the current trial population, both conditions may share some autoimmune features. Therefore assuming a smaller FVC decline of 85 mL in the placebo arm compared with 60 mL in the pirfenidone arm over the 24-week double-blind treatment period appears justified. In addition, the potential confounding effect of concomitant MMF therapy in these patients justifies stratification to ensure equal distribution of patients who receive and do not receive treatment with MMF.

6.2 SUMMARIES OF CONDUCT OF TRIAL

Patient enrollment, trial treatment administration, and reasons for early treatment discontinuation and trial discontinuation will be summarized for all enrolled patients. In addition, protocol deviations and eligibility violations will be summarized by frequency tables.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics, such as age, sex, and race, will be summarized by treatment arm using means or medians for continuous variables and proportions for categorical variables as well as appropriate measures of variability. Medical history will be tabulated by treatment arm. Summary of concomitant medications will be displayed by treatment arm in frequency tables.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this trial is to evaluate the efficacy of pirfenidone vs. placebo on lung function parameters on the basis of rate of decline in FVC in mL measured by handheld spirometry over the 24-week double-blind treatment period (see Section 2).

The primary analysis will be based on the ITT population. Patients who discontinue treatment prematurely will be analyzed based on the available data. No imputation method will be applied.

The primary analysis of the primary endpoint will compare the mean FVC decline in each treatment arm using a student's t-test with a two-sided significance level $\alpha=0.05$. The mean FVC decline for each treatment arm will be calculated using the estimated FVC decline for each individual patient. The individual FVC decline will be estimated by

applying a linear regression model to all data points collected during the 24-week double-blind treatment period.

6.4.2 Secondary Efficacy Endpoints

For secondary endpoints, all data from baseline (Day 1) until Week 24 will be taken into account for the statistical analysis. In a similar manner to the primary endpoint data, patients who discontinue early will be analyzed based on the data collected until withdrawal.

The secondary efficacy objective for this trial is to evaluate the efficacy of pirfenidone compared with placebo on the basis of the following endpoints:

- The decline of FVC in mL measured by spirometry during site (clinic) visits will be compared between the treatment arms in the same fashion as described for the primary endpoint
- Change in percent predicted FVC measured by spirometry during site visits will be compared between the treatment arms using a rank analysis of covariance (ANCOVA). Change from baseline will be used as an outcome variable and standardized rank baseline value will be used as a covariate
- Categorical changes in FVC of >5% and >10% will be compared between the treatment arms using a Cochran-Mantel-Haenszel test stratified by geographic region, concomitant MMF medication use, and the presence/absence of IPAF as defined by the MDT
- Change in percent predicted DLco will be compared between the treatment arms using a rank ANCOVA. Change from baseline will be used as an outcome variable and standardized rank baseline value will be used as a covariate
- The change in 6MWD will be analyzed using a rank ANCOVA model. The 6MWD recorded at 24 weeks will be used as an outcome variable and standardized rank baseline 6MWD will be used as a covariate
- The change in UCSD-SOBQ score will be analyzed using a rank ANCOVA model. The UCSD-SOBQ score recorded at 24 weeks will be used as an outcome variable and standardized rank baseline UCSD-SOBQ score will be used as a covariate
- The change in Leicester Cough Questionnaire score will be analyzed using a rank ANCOVA model. The Leicester Cough Questionnaire score recorded at 24 weeks will be used as the outcome variable and standardized rank baseline Leicester Cough Questionnaire score will be used as a covariate
- The change in cough visual analog scale will be analyzed using a rank ANCOVA model. The result recorded at 24 weeks will be used as the outcome variable and the standardized rank baseline result will be used as a covariate
- The change in total and sub-scores of the SGRQ will be analyzed using a rank ANCOVA model. The scores recorded at 24 weeks will be used as outcome variables and the standardized rank baseline scores will be used as covariates
- All-cause non-elective hospitalization and respiratory non-elective hospitalization will be analyzed using Kaplan-Meier techniques and the two treatment arms will be

compared with a log-rank test. In addition, hazard ratios and corresponding 95% confidence interval (CI) will be calculated by applying Cox-proportional hazard models

- The incidence of investigator reported acute exacerbations in the two treatment arms will be compared with Fisher's exact test
- PFS, defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD, or death from any cause, will be analyzed using Kaplan-Meier techniques and the two treatment arms will be compared with a log-rank test. In addition, hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models
- An alternative definition of PFS, namely the time to the first occurrence of a >10% relative decline in FVC, non-elective respiratory hospitalization, or death, will be analyzed using Kaplan-Meier techniques and the two treatment arms will be compared with a log-rank test. In addition, hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models
- Time to death from any cause and time to death from respiratory diseases will be analyzed using Kaplan-Meier techniques and the two treatment arms will be compared with a log-rank test. In addition, hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models.

For all secondary endpoints p-values will be reported in a descriptive fashion. No multiplicity adjustments for statistical testing will be done.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of trial treatment, with patients grouped according to treatment received.

The safety objective for this trial is to evaluate the safety of pirfenidone vs. placebo (see Section 2).

The safety analysis will involve investigating the nature, frequency, severity, and timing of treatment-emergent adverse events. The specific parameters that will be investigated include all adverse events, adverse events Grade ≥3 according to the NCI CTCAE version 4.0, adverse events of special interest, and serious adverse events. The primary interest in this trial will be adverse events Grade ≥3 related to pirfenidone or placebo.

Prior to the first administration, only serious adverse events caused by a protocol-mandated intervention will be recorded. These adverse events will be listed.

The incidence, type, and severity of adverse events will be summarized according to the primary System Organ Class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Adverse events Grade ≥3, adverse events of special interest, and serious adverse events will be analyzed in a similar way to all adverse events.

Descriptive statistics will be presented for dose reductions and treatment interruptions. Adverse events leading to treatment interruption or dose reduction will also be summarized.

Laboratory parameters including hematology and the chemistry panel will be presented in shift tables of NCI-CTCAE version 4.0 grade at baseline versus worst grade during treatment period. The laboratory parameters will presented according to means, standard deviation, minimum, and maximum. Selected laboratory parameters will be also graphically presented over time.

The results from the 12-lead ECGs will be summarized and presented.

The number of patients who withdraw from pirfenidone or placebo treatment with corresponding reason for withdrawal will be summarized and listed. The discontinuation from trial data will be also summarized and listed.

6.6 EXPLORATORY ANALYSES

The exploratory objectives for this trial are to evaluate the role of MMF treatment in ILD and to investigate potential biomarkers associated with fibrosis and ILD (see Section 2).

For the MMF objective, efficacy and safety data will be investigated by means of a subgroup analyses that stratifies patients according to whether they received MMF treatment. The conduct of these analyses will be described in detail in the Statistical Analysis Plan (SAP).

For the biomarker objective, assessments of the exploratory biomarkers and their relationship with drug responses will be described in a separate analysis plan.

6.7 INTERIM ANALYSIS

6.7.1 Optional Interim Analysis

There are no planned interim efficacy analyses for this trial.

Safety interim analyses will be performed at least three times during the trial, at approximately 6, 12, and 18 months after the start of recruitment.

Efficacy data will only be provided if requested by the iDMC.

Further details on the function and logistics of the iDMC will be provided in the iDMC Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this trial. A CRO will be responsible for data management of this trial, including quality checking of the data. Data entered

manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this trial, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the trial data will be consistent with the CRO's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the trial, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the trial records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Trial monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and site charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete,

microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before trial initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The trial site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a trial site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this trial and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the trial or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This trial will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). If the US participates in this trial, studies conducted in the US or under a US Investigational New Drug (IND) application will comply with US Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or EEA will comply with the European Union Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Biomarker Informed Consent Form) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final approved IRB/EC Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the trial. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the trial.

The Consent Forms should be revised whenever there are changes to trial procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the trial. For any updated or revised Consent

Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the trial.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's trial file or in the site file and must be available for verification by trial monitors at any time.

If sites in the US participate in this trial, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the US Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply, except that IRB review and approval may not be required per trial site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the trial is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the trial to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's trial file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the trial through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this trial is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization

for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to trial investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on trial data publication (see Section 9.5).

Data generated by this trial must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each trial site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial (trial completion is expected to occur approximately 84 weeks after the last patient is enrolled and receives their first dose of trial treatment).

9. TRIAL DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 TRIAL DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the trial, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to the data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of trial data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this trial.

9.4 ADMINISTRATIVE STRUCTURE

An iDMC will review safety data and advise on trial conduct (see Section 3.1). The procedures that will be used by the iDMC will be detailed in an iDMC charter. The IxRS system will be used to conduct the randomization process (see Section 4.2) and to confirm the shipment condition and content of the IMPs (see Section 4.3.3). A CRO will be responsible for data management of this trial (see Section 7.1).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of trial results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

http://www.roche.com/dam/jcr:1c46aa73-cea0-4b9b-8eaa-e9a788ed021b/en/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this trial may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of

the trial in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this trial will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Antoniou KM, Margaritopoulos GA, Tomassetti S, Bonella F, Costabel U, Poletti V. Interstitial lung disease. Eur Respir Rev 2014;23:40–54.

Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005;171:1040–7.

du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011;184:1382–9.

Chartrand S, Swigris JJ, Stanchev L, Lee JS, Brown KK. Clinical features and natural history of interstitial pneumonia with autoimmune features: A single center experience. Respiratory Medicine 2016;119:150-154.

Clarke DL, Carruthers AM, Mustelin T, Murray LA. Matrix regulation of idiopathic pulmonary fibrosis: the role of enzymes. Fibrogenesis Tissue Repair 2013;6:20.

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194:265–75.

Cottin V, Wells A. Unclassified or unclassifiable interstitial lung disease: confusing or helpful disease category? Eur Respir J 2013;42:576–9.

EMA. CHMP assessment report: Esbriet. International nonproprietary name: pirfenidone. 16 December 2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Conclusion/human/002154/WC500159531.pdf. Last accessed: 03 August 2016

Esbriet SmPC. Esbriet 267 mg hard capsules. Summary of Product Characteristics. Last updated: 11 September 2015. Available from: http://www.medicines.org.uk/emc/medicine/29932. Last accessed: 03 August 2016

Fischer A, Brown KK, du Bois RM, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol 2013;40:640–6.

Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976–87.

Health Canada. Esbriet. Last updated: 27 May 2016. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_esbriet_153849-eng.php. Last accessed: 03 August 2016

Jones RM, Hilldrup S, Hope-Gill BD, Eccles R, Harrison NK. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough 2011;7:2.

Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough 2010;6:4.

Khanna D, Albera C, Fischer A, et al. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. J Rheumatol 2016;epub.

King Jr. TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.

Leung SC, Churg AM, Leipsic JA, Levy RD, Wilcox PG, Ryerson CJ. Unclassifiable interstitial lung disease: an unresolved diagnostic dilemma. Respirol Case Rep 2015;3:85–8.

Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. The Lancet 2011;377:1760–9.

Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: Different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol 2008;590:400–8.

Panopoulos ST, Bournia V-K, Trakada G, Giavri I, Kostopoulos C, Sfikakis PP. Mycophenolate versus cyclophosphamide for progressive interstitial lung disease associated with systemic sclerosis: a 2-year case control study. Lung 2013;191:483–9.

Raghu G, Anstrom KJ, King Jr. TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968–77.

Russell A-M, Adamali H, Molyneaux PL, et al. Daily home spirometry: an effective tool for detecting progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2016;epub.

Ryerson CJ, Urbania TH, Richeldi L, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J 2013;42:750–7.

Ryerson CJ, Cayou C, Topp F, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: A prospective cohort study. Respir Med 2014;108:203–10.

Ryu JH, Moua T, Daniels CE, et al. Idiopathic pulmonary fibrosis: evolving concepts. Mayo Clin Proc 2014;89:1130–42.

Schaefer CJ, Ruhrmund DW, Pan L, Seiwert SD, Kossen K. Antifibrotic activities of pirfenidone in animal models. Eur Respir Rev 2011;20:85–97.

Skolnik K, Ryerson CJ. Unclassifiable interstitial lung disease: A review. Respirology 2016;21:51–6.

Solomon JJ, Ryu JH, Tazelaar HD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med 2013;107:1247–52.

Spagnolo P, Tonelli R, Cocconcelli E, Stefani A, Richeldi L. Idiopathic pulmonary fibrosis: diagnostic pitfalls and therapeutic challenges. Multidiscip Respir Med 2012;7:42.

Swigris JJ, Wamboldt FS, Behr J, et al. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax 2010;65:173–7.

Swigris JJ, Han M, Vij R, et al. The UCSD shortness of breath questionnaire has longitudinal construct validity in idiopathic pulmonary fibrosis. Respir Med 2012;106:1447–55.

Takeda Y, Tsujino K, Kijima T, Kumanogoh A. Efficacy and safety of pirfenidone for idiopathic pulmonary fibrosis. Patient Prefer Adherence 2014;8:361–70.

Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:821–9.

Todd NW, Luzina IG, Atamas SP. Molecular and cellular mechanisms of pulmonary fibrosis. Fibrogenesis Tissue Repair 2012;5:11.

Tzouvelekis A, Galanopoulos N, Bouros E, et al. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: a meta-analysis. Pulm Med 2012;2012:143637.

US FDA. US Food and Drug Administration package insert. ESBRIET® (pirfenidone) capsules, for oral use. Last updated: September 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022535s001lbl.pdf. Last accessed: 03 August 2016

Volkmann ER, Tashkin DP. Treatment with systemic sclerosis-related interstitial lung disease: a review of existing and emerging therapies. Annals of the American Thoracic Society;2016:1-43.

Appendix 1 Schedule of Assessments

	Washout [a]	Screening	Double-blind treatment							Early treatment discontinuation [b]	Follow-up[u]	Additional safety follow-up [c]	Additional safety follow-up final visit
Day Week	–50 to –22	–21 to –1	Randomization 1 1	28 4	56 8	84 12	112 16	140 20	168 24		196 28	up to 12 months	up to 12 months plus 28 days
Window (days, unless otherwise stated)				±5	±5	±5	±5	±5	±5	±5 [b]	±5	±5	±5
Treatment Period Visit			1	2	3	4	5	6	7			Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
Informed consent [d,e]	x	x											
Review Eligibility Criteria		x											
Demographic data [e]	x	x											
General medical history and baseline conditions [e]	x	x											
Vital signs [f]		x	x	x	x	x	x	x	x	x	x	x	
Weight		x							x	x			
Height		x											
Complete physical examination [g]		x	x						x	x			

	Washout [a]	Screening	Double-blind treatment							Early treatment discontinuation [b]	Follow-up[u]	Additional safety follow-up [c]	Additional safety follow-up final visit
Day Week	–50 to –22	–21 to –1	Randomization 1 1	28 4	56 8	84 12	112 16	140 20	168 24		196 28	up to 12 months	up to 12 months plus 28 days
Window (days, unless otherwise stated)				±5	±5	±5	±5	±5	±5	±5 [b]	±5	±5	±5
Treatment Period Visit			1	2	3	4	5	6	7			Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
ECG [h]		x	x			x			x	x	x		
Hematology [i]		x	x			x			x	x			
Chemistry [j]		x	x	x	x [k]	x	x [k]	x [k]	x	x		x[k]	
Pregnancy test [l]		x	x	x	x	x	x	x	x	x		x	
Trial treatment administration			x	x	x	x	x	x			x [m]	x	
Spirometry (FVC, FEV_1)		x	x	x	x	x	x	x	x	x			
Daily spirometry (handheld device) [n,o]		x	x	x	x	x	x	x	x	x			
DLco		x	x			x			x	x			
6MWD [p]		x	x			x			x	x			
Leicester Cough Questionnaire [q]			x			x			x	x			
UCSD-SOBQ [q]			x			x			x	x			

	Washout [a]	Screening	Double-blind treatment							Early treatment discontinuation [b]	Follow-up[u]	Additional safety follow-up [c]	Additional safety follow-up final visit
Day Week	–50 to –22	–21 to –1	Randomization 1 1	28 4	56 8	84 12	112 16	140 20	168 24		196 28	up to 12 months	up to 12 months plus 28 days
Window (days, unless otherwise stated)				±5	±5	±5	±5	±5	±5	±5 [b]	±5	±5	±5
Treatment Period Visit			1	2	3	4	5	6	7			Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
SGRQ [q]			x			x			x	x			
Cough visual analog score [q]			x			x			x	x			
Serum for biomarker assessments			x	x		x			x	x			
Plasma for biomarker assessments			x	x		x			x	x			
Whole blood for *PAX* gene biomarker assessment			x	x		x			x	x			
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [s]		x	x	x	x	x	x	x	x	x	x	x	x
Whole blood sample for RBR (optional) [t]			x										

6MWD=6-minute walk distance; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DLco=diffusing capacity of the lung for carbon monoxide; ECG=electrocardiogram; eCRF=electronic case report form; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LFT=liver function test; PRO=patient-reported outcome; RBC=red blood cell; RBR=Research Biosample Repository; SGRQ=St. George's Respiratory Questionnaire; SOBQ=Shortness of Breath Questionnaire; UCSD=University of California, San Diego; WBC=white blood cell

Notes: all assessments should be performed within 7 days of the scheduled visit, unless otherwise specified.

[a] Patients will be required to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period. Patients not taking a prohibited medication will forgo the washout period and directly enter screening.

[b] Patients who discontinue trial treatment prematurely will return to the site (clinic) for an Early Treatment Discontinuation Visit 28 (± 5) days after the last dose of the double-blind treatment, thus ending their participation in the trial. For patients who end their participation in the double-blind treatment period due to unblinding, they may be offered to continue into the open-label period according to the investigator's judgment. These patients will attend the Early Treatment Discontinuation Visit (28 (± 5) days after the last dose of the double-blind treatment) and on the same day begin their participation in the 12-month open-label pirfenidone safety follow-up period.

[c] After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the 12-month safety follow-up period, initially, patients will be evaluated at monthly visits for the first 6 months. At the end of the first 6 months, patients will be evaluated at each site visit occurring approximately every 3 months until the end of the safety follow-up period.. A final Follow-up Visit will be performed at the end of the safety period, 28 (± 5) days after the last open-label dose.

[d] Informed consent must be documented before any trial-specific screening procedure is performed, and may be obtained either at the Washout or Screening Visits.

[e] Any procedures that were not completed during washout, must be completed at the Screening Visit.

[f] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF. All vital sign measurements are to be obtained prior to any blood draws scheduled at the same time.

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

[h] All ECGs are to be obtained prior to other procedures scheduled at the same time.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH.

[k] Only LFTs (AST, ALT, bilirubin, and alkaline phosphatase) will be conducted at these visits. During the Safety Follow-up period, LFTs will be performed every month during the first 6 months and subsequently at each visit occurring approximately every 3 months thereafter, until the end of this period.

[l] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at the specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During the Safety Follow-up period, urine pregnancy tests will be performed every month during the first 6 months at each site visit. Urine pregnancy tests will continue to be performed on a monthly basis during the remainder of the Safety Follow-up period with patients performing the test at home (using kits provided by the site) during months where there is no site visit and at each site visit occurring approximately every 3 months. Patients will be instructed to contact the site immediately in case the result of the home pregnancy test is positive. In such cases, the patient must visit the site for a confirmatory serum pregnancy test.

[m] Open-label treatment with pirfenidone will be started at this visit, if the patient requests continued treatment with pirfenidone.

[n] Handheld spirometry will be conducted by the patient every day in a seated position.

[o] To provide handling evaluations and quality assurance for the daily spirometer assessments, nursing visits to the patient's home (or at another suitable location) will occur at least three times during the trial, namely between Weeks 1 and 4, between Weeks 8 and 12, and between Weeks 16 and 20. Additional home nursing visits may be conducted according to the investigator's judgment.

[p] 6-Minute Walk Distance (6MWD) is used to evaluate the functional capacity of patients with lung disease.

[q] Questionnaires will be self-administered prior to the patient receiving any information on disease status and prior to the performance of non-PRO assessments. Refer to Appendix 2 for copies of the questionnaires and a brief description.

[r] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from the washout period until 28 days after the last dose of trial treatment.

[s] After informed consent has been obtained but prior to initiation of trial treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of trial treatment, all adverse events will be reported until 28 days after the last dose of trial treatment. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior trial treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to trial treatment or trial-related procedures until a final outcome can be reported.

[t] Not applicable for a site that has not been granted approval for RBR sampling.

[u] If a patient discontinues the trial between weeks 24 and 28, final assessments according to the Follow-up visit for week 28 should be performed.

Appendix 2 Patient-Reported Outcome Questionnaires

The Leicester Cough Questionnaire is a patient-reported questionnaire evaluating the impact of cough on quality of life. The questionnaire comprises 19 items and takes 5 to 10 minutes to complete. Each item assesses symptoms, or the impact of symptoms, over the last 2 weeks on a seven-point Likert scale. Scores in three domains (physical, psychological and social) are calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) is also calculated by adding the domain scores together. Higher scores indicate better quality of life.

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of your cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by phlegm production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Sometimes	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 2 weeks, how many times a day have you had coughing fits?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversations or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

The University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ) is a symptom-specific, 24-item, patient-self-administered questionnaire that assesses shortness of breath while doing a variety of activities of daily living.

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

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

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

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

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

Harry has felt moderately short of breath during the past 7 days while brushing his teeth and so circles a three for this activity.

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

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past 7 days. She circles a five for this activity.

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

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

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

10. Showering/bathing **0 1 2 3 4 5**

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

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

11. Dressing **0 1 2 3 4 5**

12. Picking things up and tidying up a room **0 1 2 3 4 5**

13. Doing the dishes **0 1 2 3 4 5**

14. Sweeping/vacuuming **0 1 2 3 4 5**

15. Making the bed **0 1 2 3 4 5**

16. Shopping **0 1 2 3 4 5**

17. Doing laundry **0 1 2 3 4 5**

18. Washing the car **0 1 2 3 4 5**

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

20. Watering the lawn **0 1 2 3 4 5**

21. Sexual activities **0 1 2 3 4 5**

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

How much do the following limit you in your daily life?

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

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify health-related health status in patients with chronic airflow limitations.

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 3 months.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:

- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days</u>.

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

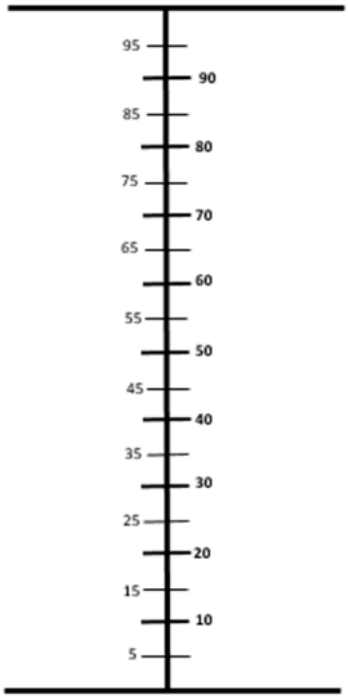
Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Cough Visual Analogue Scale (VAS)

This visual analogue scale is designed to help us learn about the severity of your cough. This scale is 100mm (10cm) in length.

During the last week, how do you rate the severity of your cough; 0mm representing no cough and 100mm representing the worst cough ever? Please indicate the severity of your cough by placing an **X** on the line.

Worst Cough ever (100mm)



No Cough (0mm)

Score:_____ mm