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STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN AMENDMENT
RATIONALE

The following changes were made compared to the first version of the SAP:

Version	Date	Change number	Change description
2	08-Oct-2018	1	Clarification related to the aim and timeline of the primary analysis and final analysis of the study are included under section Outcome Measures.
2	08-Oct-2018	2	Week 28 is included in all descriptive efficacy tables.
2	08-Oct-2018	3	The safety follow-up period definition is changed as stated in section On-treatment Assessments (12-Month Safety Follow-up Period).
2	08-Oct-2018	4	Disposition is updated in section Patient Disposition.
2	08-Oct-2018	5	Details were added in order to analyze valid daily spirometry data in section Demographic and Baseline Characteristics.
2	08-Oct-2018	6	Additional analyses needed in the safety follow-up period based on safety follow-up population are presented under section Safety Follow-up analyses.
2	08-Oct-2018	7	Safety follow-up visits were included under section Visit Windows.
2	08-Oct-2018	8	Listings of stratification factors, separated types of adverse events and pregnancy data were removed from the corresponding sections.
3	18-Jun-2020	9	Categorical change of 5% and 10% for home FVC measurements deleted because of implausible data collected
3	18-Jun-2020	10	Restrict analysis of oxygen requirements to patients who had oxygen requirements
3	18-Jun-2020	11	Add information about sensitivity analyses performed for home FVC measurements in section Sensitivity Analyses
3	18-Jun-2020	12	Add correlation analysis for home FVC and site FVC measurements (Additional analyses after FDA feedback), see Exploratory Efficacy Endpoints
3	18-Jun-2020	13	Mixed model analysis added for home spirometry and site spirometry as sensitivity analysis in section Sensitivity Analyses

3	18-Jun-2020	14	Subgroup analysis for biopsy taken before randomization (yes/no) added
3	18-Jun-2020	15	Tipping point analysis added for various assumptions to impute missing values in section Sensitivity Analyses for missing data
3	18-Jun-2020	16	Safety tables added to compare study data with phase III studies in section Adverse events

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LIST OF ABBREVIATIONS

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
BP	blood pressure
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
CSP	clinical study protocol
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
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
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

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 mycophenolate acid
NAC	N-acetyl-cysteine
NCI	National Cancer Institute
NGS	next-generation sequencing
NSIP	nonspecific interstitial pneumonia
PDGF	platelet-derived growth factor
PDMS	protocol deviation management system
PFS	progression-free survival
PFTs	pulmonary function tests
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cells
RBR	Research Biosample Repository
RNA	ribonucleic acid
RoW	Rest of the World
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SGRQ	St. George's Respiratory Questionnaire
SOBQ	Shortness of Breath Questionnaire
SOC	System Organ Class
SOP	standard operating procedure
SpO2	oxyhemoglobin saturation at rest
SQRT	Square root

SSc	systemic sclerosis
TEAE	treatment-emergent adverse event
TGF	transforming growth factor
TID	three times daily
UCSD	University of California, San Diego
UIP	usual interstitial pneumonia
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale
VC	vital capacity
WBC	white blood cells
WGS	whole genome sequencing

1. BACKGROUND

As described in section 1.3 of Clinical Study Protocol (CSP) version 2.0 dated 3 March 2017, no approved treatments are available for the 15% of patients with interstitial lung disease (ILD) who have unclassifiable disease. 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 idiopathic pulmonary fibrosis (IPF) are sufficiently encouraging 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 (Esbriet®) 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.

Mycophenolate mofetil/sodium or mycophenolic acid (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. 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. STUDY DESIGN

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 multidisciplinary team (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.

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.

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 CSP) 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 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. 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 CSP 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. 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, patients will be given the opportunity to receive open-label pirfenidone within a safety follow-up period of up to 12 months of the 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. 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.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1 and the Schedule of Assessments in Appendix 2 For additional details, please see the CSP Version 3, 28 June 2018 (and its Appendices).

2.2 OUTCOME MEASURES

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).

The primary analysis of the primary and secondary efficacy outcome measures of this study is planned to be performed when the last patient reached the date of the last follow-up visit after end of the double-blind treatment period.

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy objective for this trial is to evaluate the effect of pirfenidone vs. placebo on lung function parameters on the basis of Forced Vital Capacity (FVC) measurements. FVC will be measured daily by the patients by use of a handheld spirometry.

The primary efficacy endpoint is defined as:

- rate of decline in FVC in mL measured by daily handheld spirometer over the 24-week double-blind treatment period.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy objective for this trial is to evaluate the efficacy of pirfenidone compared with placebo from baseline until Week 24 on other functional parameters, outcomes, and patient reported outcomes (PROs).

The following endpoints will be analyzed:

- 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 by spirometry during clinic visits
- Categorical change in FVC of >10% (absolute change in percent predicted and relative change in mL), measured by spirometry during clinic visits
- Change in percent predicted diffusing capacity of the lung for carbon monoxide (DLco)
- Change in (6-minute walk distance) 6MWD in meters
- Change in University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) score
- Change in score in Leicester Cough Questionnaire
- Change in cough visual analog scale
- Change in total and sub-scores of the St. George's Respiratory Questionnaire (SGRQ)
- Non-elective hospitalization, both respiratory and all cause
- Incidence of, and time to first, investigator-reported acute exacerbations
- Progression free survival (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

2.2.3 Exploratory Efficacy Outcome Measures

One exploratory objective for this trial is to evaluate the role of mycophenolate mofetil/sodium or mycophenolic acid (MMF) treatment in ILD and to evaluate potential biomarkers associated with fibrosis and ILD.

The exploratory endpoints associated are:

- Efficacy and safety data from subgroups of patients who did or did not receive MMF treatment
- Biomarker data from plasma, serum, and whole blood ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) samples

2.2.4 Safety Outcome Measures

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

- 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

All analyses with regard to the safety outcome measures will be performed from the date of first randomized treatment intake until 28 days after the last positive dose during the double-blind randomized treatment period.

2.3 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.

2.4 INTERIM ANALYSIS

There are no planned interim efficacy analyses for this trial.

3. STUDY CONDUCT

The study conduct is described in Section 2.

3.1 RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURES

Patients will be randomized 1:1 to receive either pirfenidone or 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 arm, 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 CSP 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.

3.2 INDEPENDENT REVIEW FACILITY

An independent review of home spirometry date (FVC (mL)) took place after it was recognized that the data collected for the primary analysis of this study was jeopardized by incorrect readings of the device and implausible values were collected due to technical issues. A new data set is available now after doing the reread of the FVC data and will be analyzed together with the previous data set collected to investigate the impact of the new data on the statistical results of this endpoint.

More details are provided in section 4.5.2.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review safety data and advice on study conduct at least three times during the study. Efficacy data will only be provided if requested by the iDMC. A first meeting is planned 6 months after start of recruitment, and subsequently at 12 and 18 months. Details on procedures and safety review by the iDMC are described within an iDMC charter.

4. STATISTICAL METHODS

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate). Percentages will be based on the number of patients in each treatment arm for the analysis population, if not otherwise specified.

Continuous endpoints will be summarized using descriptive statistics (mean, standard deviation, minimum, 25th and 75th quartiles, median, and maximum).

Where data will be summarized over time, the following timepoints will be presented as applicable: Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28 (if applicable) and early discontinuation visit.

Data analysis of data collected during the 12-month safety follow-up period will be described in section 4.7.

Where applicable other analysis methods will be specified below.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-treat Population

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in the ITT population will be assigned to treatment arm as randomized (planned treatment). The ITT population is the primary analysis population for all efficacy analyses. The time period for all efficacy analyses is defined from date of randomization until the treatment completion date of the double-blind treatment period or the date of early discontinuation collected on the early treatment discontinuation eCRF page in case a patient does not complete the planned 24 weeks of double-blind treatment.

4.1.2 Per Protocol Population

Not applicable.

4.1.3 Safety Population

The safety population is defined as all patients with at least one intake of pirfenidone or placebo, i.e. at least one record in the drug-log of the double-blind period with a non-zero dose. Patients in the safety population will be assigned to treatment arm according to the actual treatment they received.

4.1.4 Safety Follow-up Population

For the 12-month safety follow-up period, the safety follow-up population will be defined as all patients who have received at least one dose of pirfenidone after the randomized treatment end plus 28 days.

Safety analyses for the 12-month follow-up period will be performed from the date of the first pirfenidone drug intake during safety follow-up period up to the study completion/discontinuation visit.

4.2 TRIAL PERIODS, OBSERVATION AND ANALYSIS TIMES

Where durations are to be calculated (e.g. treatment duration), these will be derived based on the interval in days (end date – start date + 1) and converted to months and years if needed, using 30.4375 and 365.25, respectively, as denominator if not otherwise specified.

For the investigational medicinal product (IMP) exposure, treatments administered from the date of first randomized pirfenidone/placebo treatment up to the date of completion of double-blind treatment or date of early treatment discontinuation, will be regarded.

For drug safety, analyses will be restricted to AEs or assessments that occurred from the first day of randomized treatment until the date of last positive dose of randomized treatment plus 28 days.

Safety analyses for the 12-month follow-up period will be performed using the time window from the safety follow-up period start up to the study completion/discontinuation visit.

4.2.1 Study Days

Study days will be defined as the number of days since randomization, and is calculated as:

- Study day = Assessment date – randomization date + 1, for assessments on or after the randomization date.
- Study day = Assessment date – randomization date, for assessments before the randomization date.

The day of randomization will be study day 1.

4.2.2 Baseline and Screening Observations

Table 1 Definition of Baseline and Screening Observations

	Definition
Baseline data	Baseline is defined as the last valid assessment prior to first intake of randomized study drug (pirfenidone/placebo). This may not be the same as the Day 1 (Week 1) visit as per eCRF. In case that Day 1 (Week 1) visit data is missing and the randomized treatment is given, data from the screening period will be used as baseline. In addition, if randomized treatment is not given then baseline will be defined as the last valid assessment collected either screening or day 1. Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (pirfenidone/placebo) was given. Adverse events occurring on the date of first randomized pirfenidone/placebo treatment will not be considered baseline, but treatment-emergent.
Screening data	Screening measurements are all the measurements performed before the randomization date.

4.2.3 On-treatment Assessments for Efficacy Analyses (Double-blind Treatment Period)

For efficacy analyses, on-treatment assessments will be the assessments performed on or after the randomization date until the double-blind treatment completion or discontinuation date.

4.2.4 On-treatment Assessments for Safety Analyses (Double-blind Treatment Period)

For safety analyses, on-treatment assessments will be the assessments performed on or after the first dose of randomized pirfenidone/placebo date until the last positive dose of randomized treatment plus 28 days.

4.2.5 On-treatment Assessments (12-Month Safety Follow-up Period)

Details of all data recorded during the 12-month safety follow-up period will be presented. This period starts on the day of the first positive dose of pirfenidone after the 28 days follow-up visit for patients who completed the double-blind treatment period without being discontinued the study. The safety follow-up period ends with the study completion/discontinuation visit, with a maximum duration of 12 months plus 28 days.

Safety follow-up analyses will be presented separately from double-blind treatment phase ones.

4.2.6 Cut-off points

The clinical cut-off for the primary analysis will occur when the last patient has completed the final safety Follow-up Visit, 28 days after the double-blind treatment period.

There will be a second cut-off for the final analysis when all patients have completed the 12-month safety follow-up 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) plus 28 days and a final safety Follow-up Visit 4 weeks after the last dose.

4.3 ANALYSIS OF TREATMENT ARM COMPARABILITY

To ensure the comparability of the treatment arm, the randomization will be stratified by the availability of a previous MMF treatment (yes/no) and the presence/absence of IPAF as defined by MDT to ensure an equal distribution of patients.

These stratification factors will be included in the analysis of the primary endpoint as a sensitivity analysis. Please refer to the corresponding section 4.4.5 for further details.

Outputs for concordance between the stratification factors by eCRF and by IxRS will also be presented.

4.4 ANALYSIS OF STUDY CONDUCT

Unless otherwise specified, all analyses described in this section will be performed on the ITT population, presenting data by treatment arm.

4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients enrolled, screened, failed screening, randomized, treated, completed or early discontinued the double-blind treatment period, patients entering the 12-month safety follow-up period and their current status (ongoing, completion, discontinued) in that period will be provided. For patients who have early discontinued the double-blind treatment period or the study, frequencies of reasons for early discontinuation will be provided. A listing with all the patient disposition data will be also presented.

The following definitions will be used:

- Patients randomized: All patients who have been randomized to receive either pirfenidone or placebo, i.e. have a randomization date.

- Patients randomized and not treated: all randomized patients who have not received at least one dose of the randomized treatment.

- Patients randomized and treated: all randomized patients who have received at least one dose of the randomized treatment.

- Patients randomized and treated with sufficient post-baseline efficacy data: all randomized patients who have received at least one dose of the randomized treatment and have at least one post-baseline assessment of FVC (mL).

- Completion of double-blind treatment period: eCRF question “Did the patient complete course of double-blind treatment?” is ticked “Yes” (eCRF form “Double-blind treatment Completion/Early Discontinuation”).

- Early discontinuation (non-completion) of double-blind treatment period: eCRF question “Did the patient complete course of double-blind treatment?” is ticked “No” (eCRF form “Double-blind treatment Completion/Early Discontinuation”).

- Early discontinuation (non-completion) of study: eCRF question “Did the subject early discountinue from the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”) for patients who discontinued double-blind treatment period.

- Status during the 12-month safety follow-up (entered, ongoing, completed). Completers are defined as those patients that have filled the study completion/discontinuation form. Otherwise, the patient is considered ongoing in the safety follow-up phase.

- Completion of study: eCRF question “Did the subject complete the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”)

- Early discontinuation (non-completion) of study: eCRF question “Did the subject early discountinue from the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”)

An overview on patients’ enrolment will be provided based on the randomized subjects by country and center separately for the pirfenidone and placebo arm.

Kaplan-Meier (KM) plots for time to treatment discontinuation will be provided for all randomized patients and by randomized arm, based on the date subject completed or early discontinued from double-blind treatment period, as per eCRF. If the patient completed the treatment without treatment discontinuation, then it will be censored to the date of treatment completion.

In addition, KM plots for time to study discontinuation will be presented for all randomized patients by arm, based on the study discontinuation date. If the patient completed the study as planned per protocol, then the patient will be censored to the study completion date.

In addition, a consort diagram with some of the categories above will be presented.

4.4.2 Major Protocol Deviations

Major protocol deviations and eligibility violations will be summarized by frequency tables and all patients with protocol deviations will be listed. Protocol deviations will be collected in the protocol deviation management system (PDMS), reviewed by the medical monitors. All deviations provided in that dataset will be considered as major protocol deviations.

4.4.3 Demographic and Baseline Characteristics

Baseline and disease characteristics such as demographics, medical history and tobacco use history will be summarized by descriptive statistics or frequency tables for each treatment arm.

Demographics

The following demographic characteristics will be summarized by treatment arm:

- Age (years): as entered in the eCRF at the screening visit.
- Age categories: <65, and ≥ 65.
- Age categories: <45, ≥45 to <65 years, ≥65 to <85 years, and ≥ 85 years.
- Gender: Male/Female.
- Race: White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Unknown. In case that more than one race will be ticked, a concatenated variable, containing all races will be presented (e.g. Asian/White).
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown.
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m2) at baseline. BMI will be calculated as: weight(kg) / (height(m))2
- Female reproductive status: childbearing potential without contraceptive protection, Childbearing potential with contraceptive protection, surgically sterilized, Postmenopausal, Pre-menarchal, Non childbearing potential.

Data on female reproductive status will be presented descriptively.

Demographic data will be also listed.

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 20.1 or higher and will be summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT) by treatment arm. If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

A listing with past and ongoing medical history data from the washout period will be presented.

Tobacco use history

The history of tobacco use will be summarized by treatment arm with the following characteristics:

- Tobacco use history (never, current, previous)
- Nicotine exposure (pack-years), smokers only

Numbers and percentages of patients will be provided for tobacco use history. Nicotine exposure will be summarized descriptively.

Diagnosis and time from uILD Diagnosis

Frequencies and percentages will be presented for the uILD category collected into the eCRF page MDT/Diagnosis (Eligibility).

The time in months since the original uILD diagnosis will be calculated as

Date of randomization – Date of ILD diagnosis and will be summarized descriptively by randomized treatment arm. The number and percentage of patients with a historical high-resolution computed tomography and with a historical surgical lung biopsy will also be presented.

Descriptive statistics of the time from most recent historical high-resolution computed tomography (months) and historical surgical lung biopsy will be presented. As above, the date of randomization will be used as reference date for calculation of duration.

Stratification Factors

The number and percentage of patients that fall into each of the four groups based on the two stratification factors: Concomitant MMF treatment (yes/no), and the presence/absence of IPAF as defined by the MDT will be presented by treatment arm.

Baseline Site Spirometry Test

The values recorded for the baseline assessments of the site spirometry tests were the following:

- Forced vital capacity (FVC) (L and % predicted)
- Forced expiratory volume in 1 second (FEV1) (L and % predicted)
- FEV1 (L) / FVC (L) ratio (1)
- Carbon monoxide diffusing capacity (DLco) (% predicted)

Descriptive statistics will be provided for these parameters separately for treatment arm.

Historical Spirometry Test

The number and percentage of patients who performed spirometry test (FVC, DLco, FEV1, and FEV1/FVC ratio) in the past will be provided. The most recent assessment before the Screening visit will be collected:

- Hemoglobin corrected DLco (mmol/min/kPa and %)
- DLco/Va (KCO) (mL/min/mmHg/L and % predicted)
- FVC (L and % predicted)
- FEV1 (L and % predicted)
- FEV1(L)/FVC(L) ratio (1)

These historical spirometry test parameters will be summarized using descriptive statistics by treatment arm. Both, absolute and percent predicted values will be presented. Frequencies and percentages will be presented for the high-resolution computed tomography and the surgical lung biopsy.

Baseline 6-minute walk distance (6MWD)

The 6MWD is used to evaluate the functional capacity of patients with lung disease. The 6MWD measures the distance a patient is able to walk quickly on a flat, hard surface in a period of 6 minutes.

The number and percentage of patients that

- Performed the 6-minute walking test (yes/no),
- Rested for at least 10 minutes (yes/no),
- Stopped the test before 6 minutes (yes/no),
- Required O2 (yes/no)

at the baseline visit will be summarized by randomized treatment group.

The values of the parameters recorded for the 6MWD test are:

- Vital signs (Heart rate (beats/min), systolic blood pressure (mmHg), diastolic pressure (mmHg)) (before the test, at the end of the test)
- Distance walked (m),
- Oxyhemoglobin saturation (SPO2) (before the test (at rest), at the end of the test),
- Oxygen (O2) requirements (L) for patients who received oxygen (at the end of the test)

will be summarized descriptively by treatment arm.

4.4.4 Previous and Concomitant Medication

Previous and concomitant medications will be presented based on the safety population. Post medications administrated during the safety follow-up period will be presented based on the safety follow-up population.

Previous and concomitant medications are non-study medications. Concomitant therapy includes any medication used by a patient from the washout period until 28 days after the last dose of trial treatment. The previous and concomitant medication will be coded using the Genentech (GNE) drug dictionary. This is a proprietary Roche Dictionary which is used to code concomitant medications in the Trial Management System (TMS) coding tool. The Standardized Medication Name (CMDECOD), which is the medication generic or combination generic as defined by the Drug Thesaurus (proprietary Genentech/Roche dictionary), and the Medication Class (CMCLAS), which is the primary medication class as defined by the Drug Thersaurus, will be used for the analyses.

Therapies will be classified as previous or concomitant as follows:

Previous: If the medication start date is prior to start of double-blind treatment,

Concomitant: If medication is taken at any time between the start of double-blind treatment and 28 days after last positive dose of randomized treatment.

Post (safety follow-up): If the medication is taken more than 28 days after the last positive dose of randomized treatment.

The number and frequency of previous and concomitant medications taken by patients in the two treatment arms will be presented by Medication Class and Standardized Medication Name. If patients receive more than one drug within a Medication Class or Standardized Medication Name they will be counted only once for the respective Medication Class or Standardized Medication Name.

A separated table will be presented for post medications during the safety follow-up period.

All medications will be listed identifying the previous/concomitant and post medications.

The missing imputation rules for the medication dates are described under Section 4.9..

4.4.5 Daily Spirometry (Handheld Device)

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. The following blow categories will be collected:

Quality description	Acceptable text
Accepted	YES
Rejected	NO
Borderline Accepted	BOR

Only accepted blows will be considered for the analysis. If one patient has more than one measurement per day, the last measurement will be taken.

FVC (mL) will be measured daily with a handheld device.

After primary analysis of study data it was detected that FVC values from home spirometry were impacted by high variability and implausible values were accepted by the system. In order to evaluate the issue a re-read of home spirometry data will be performed and the new dataset with modified flagging of acceptable values will be analyzed in the same way as described below for the primary endpoint, see also 4.5.2.

4.4.6 Compliance

With respect to the home-based daily measurements compliance of patients will be investigated. It will be analyzed if gaps of measurements occur over time. A gap is thereby defined as 7 or more than 7 consecutive days of missing measurements. A summary table displaying number of patients with gaps in daily measurements, number of gaps and duration of gaps will be provided by treatment arm for data from handheld spirometer.

4.5 EFFICACY ANALYSIS

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

The primary analysis of the primary efficacy endpoint of this study is planned to be performed when the last patient reached the date of the last follow-up visit after end of the double-blind treatment period (clinical cut-off date).

4.5.1 Primary Efficacy Endpoints

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 spirometer over the 24-week double-blind treatment period.

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 for the primary endpoint.

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 α=0.05. The mean FVC decline for each treatment arm will be calculated using the estimated FVC decline for each individual patient. The estimated FVC decline for individual patients will be obtained by applying a linear regression model to all data points collected during the 24-week double-blind treatment period:

$$X_{it} = \alpha_i + \beta_i D_{it} + u_{it}$$

where

X_{it} = the FVC measurements (mL) of patient i on day t, with i=1,…,N and t=1,…,T, being N the total number of patients randomized and T the total number of days with assessment.

D_{it} = study day t of patient i

α_i, β_i = intercept and slope of the individual linear regression of patient i

The time-adjusted decline for patient i is then obtained by estimating the patients' individual difference in predicted values between baseline and week 24 from the linear regression.

In a further step, the time-adjusted mean FVC decline is estimated by calculating the mean over all individual time-adjusted declines of all patients by treatment arm.

A summary table displaying the mean FVC decline together with two-sided 95% confidence intervals based on percentiles of the t-distribution will be provided by treatment arm. The mean FVC decline in each treatment arm will be compared using a student's t-test with a two-sided significance level α=0.05. Additionally, a two sample Wilcoxon test will be used for treatment comparison. Results of this test are of descriptive nature only.

The same analyses will be done by restricting the FVC decline values:

- Including patients with at least 3 site spirometry measurements

- excluding patients with a predicted FVC decline below -1000 mL
- or above 1000 mL
- excluding values with a difference +/-50% from corresponding baseline site spirometry

Mean FVC declines and results from Student' s t-test by subgroups (for definition see 4.5.6) will be displayed in a forest plot.

As a sensitivity analysis to the primary analysis, the time-adjusted mean FVC decline will be estimated by a repeated measures mixed model with patient effects fitted as random and day of measurement and treatment fitted as fixed effects. Please refer to Section 4.5.6 for further details.

A detailed description of SAS code to be used for the repeated measures mixed model is provided together with the respective table shell.

4.5.2 Reassessment of quality of home spirometry

Due to the nature of the home FVC measurements resulting in a highly skewed distribution with high unexpected variability and a number of measurements resulting in physiologically implausible values the home spirometry data was reassessed by an independent and blinded group of experts.

The reassessment of home spirometry data resulted in a flag with 2 categories:

130 = acceptable, 110 = not acceptable.

A comparison between the quality assessments before and after update will be presented by a concordance analysis. In this analysis old assessments with "BOR" are tabulated as non-acceptable quality.

The compliance of home spirometry data will also be assessed by analyzing the number of gaps in daily measurements.

4.5.3 Secondary Efficacy Endpoints

For secondary endpoints, all data from baseline 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 date of withdrawal from treatment.

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

- Descriptive statistics for values and changes from baseline over time of all spirometry test parameters will be presented.

- 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. A Wilcoxon tests was not planned for this endpoint.

- Mean FVC declines and results from Student' s t-test by subgroups (for definition see 4.5.6) will be displayed in a forest plot.

- In addition the decline of FVC in mL measured by spirometry during site (clinic) visits will be compared between the treatment arms using a repeated measures mixed effects model. Please refer to Section 4.5.6 for further details.

- The absolute change in percent predicted FVC measured by spirometry during site visits at week 24 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 (mL) measured during site (clinic) visits of >5% and >10% will be compared between the treatment arms using a Cochran-Mantel-Haenszel test stratified by concomitant MMF medication use (Yes/No), and the presence/absence of IPAF as defined by the MDT

- Absolute change from baseline to week 24 in percent predicted DLco will be compared between the treatment arms using a rank ANCOVA. Change from baseline to week 24 will be used as an outcome variable and standardized rank baseline value will be used as a covariate
    - A summary table presenting the values of DLco (%) and its change from baseline will be presented over time and by treatment arm.
- The absolute 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
    - A summary table presenting the 6MWD parameters and their change from baseline will be presented over time and by treatment arm.
- The absolute change in UCSD-SOBQ total score will be analyzed using a rank ANCOVA model. The UCSD-SOBQ total 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 Please see Section 4.5.5 for further details.
- The absolute change in Leicester Cough Questionnaire total score will be analyzed using a rank ANCOVA model. The Leicester Cough Questionnaire total score recorded at 24 weeks will be used as the outcome variable and standardized rank baseline Leicester Cough Questionnaire total score will be used as a covariate. Please see Section 4.5.5 for further details.

- 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. Please see Section 4.5.5 for further details.
- The change in total 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. Please see Section 4.5.5 for further details.
- The time from randomization to the first occurrence of all-cause non-elective hospitalization and respiratory non-elective hospitalization will be analyzed using Kaplan-Meier (KM) techniques:
    - KM plots of time to first occurrence of the different events will be provided by treatment arm. Frequencies and percentages of patients with events and patients censored will be provided. Descriptive statistics of KM estimates of the time to first occurrence (weeks) will be presented.
    - Log-rank tests based on the time to the first event will be used to compare the two treatment arms.
    - Hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models in which the four groups from the two randomization stratification factors are included in the model.
- The incidence of investigator reported acute exacerbations in the two treatment arms will be compared with Fisher's exact test.
    - Incidence of, and time to first, investigator-reported acute exacerbations
- Progression free survival (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:
    - KM plots of time to first occurrence of the combined primary efficacy endpoint will be provided by treatment arm.
    - Frequencies and percentages of patients with events and patients censored will be provided. Descriptive statistics of KM estimates of PFS (weeks) will be presented.
    - The PFS of two randomized treatment arms will be compared with a log-rank test.
    - Hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models.
- An alternative definition of PFS (also in weeks), 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 as

defined for the point above; 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 assessed by the SOC “Respiratory, thoracic and mediastinal disorders” (in weeks) will be analyzed using Kaplan-Meier techniques as defined above; 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.

4.5.4 Exploratory Efficacy Endpoints

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.

For the MMF objective, primary and selected secondary endpoints will be investigated by means of a subgroup analyses that stratifies patients according to whether they received MMF treatment. In addition, the overall safety summary will be presented by this subgroup. The selected secondary endpoints are:

- Deaths from any cause and respiratory disease-related
- Hospitalizations from any cause and respiratory disease-related

The analysis of these exploratory efficacy endpoints by subgroup are defined under section Section 4.5.6.

The mean FVC decline in each treatment arm will be calculated as in the primary analysis for the subgroups of patients that received MMF treatment and compared using a student’s t-test.

Other exploratory efficacy endpoints are discussed in the sensitivity and subgroup sections (see Section 4.5.6 and Section 4.5.7, respectively).

Moreover, additional categorical analyses for the percent predicted DLco and 6MWD will be presented as exploratory:

- Categorical change of >15% absolute decline from baseline to week 24 in percent predicted DLco will be compared between the treatment arms using a logistic regression.
- Categorical change of >50% absolute decline from baseline to week 24 in 6MWD (m) will be compared between the treatment arms using a logistic regression.

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

A correlation analysis of individual patient slopes estimated by linear regression models between those obtained for home spirometry and site spirometry were performed to assess the concordance of the data obtained by the two methods.

4.5.5 Analyses of 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.

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. 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.

St. George´s Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantifies health-related health status in patients with chronic airflow limitations. The SGRQ is a 50-item questionnaire, addressing the frequency of respiratory symptoms (items 1 – 8), the patient's current state (sections 9 – 16). From the 50 items a total score, as well as three component scores (Symptoms, Activities, Impacts) will be derived. The total score ranges from 0, presenting the best possible health status to 100, presenting the worst possible health status.

The change in SGRQ total score will be of primary interest when assessing health-related quality of life (HRQoL).

The analysis of PROs assessed by SGRQ total score and by SGRQ component scores for symptoms, activity, and impacts will be analyzed as follows:

- The absolute score values and changes from baseline for the total and each sub-score will be presented descriptively over time by treatment arm.
- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate. This analysis will be done only for the total score.

The SGRQ and the details for calculating the score can be found in Appendix 3.

The University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)

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. Each of the 24 activities are rated on how dyspnea affects the activity on a 6-point scale: 0 = None at all to 5 = Maximal or unable to do because of breathlessness. The scores will be summarized to a total score, ranging from 0 – 120.

The total score of the UCSD SOBQ will be summarized as follows:

- The absolute total scores and changes from baseline will be presented descriptively over time by treatment arm.
- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

Additional details on the UCSD SOBQ can be found in Appendix 3

The Leicester Cough Questionnaire

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.

The total score and the physical, psychological and social domain scores of the Leicester Cough Questionnaire will be analyzed as follows:

- The scores and changes from baseline will be presented descriptively over time by treatment arm.
- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate. This analysis will be done only for the total score.

Details on calculating the domain scores can be found in Appendix 3

The Cough VAS

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

The cough VAS score will be summarized descriptively by visit and treatment arm. The change in cough VAS will be analyzed using a rank ANCOVA model. The change in VAS score for cough recorded at 24 weeks will be used as the outcome variable and the standardized rank baseline result will be used as a covariate. Please refer to Appendix 3 for further details.

4.5.6 Sensitivity Analyses

As a sensitivity analysis to the primary analysis, the time-adjusted mean FVC decline will be estimated a random slope and intercept linear regression model, with an absolute change in FVC (mL) as the outcome variable assuming linear decline in lung function over time. The model includes random coefficients for slope and intercept and fixed effect terms for treatment, and covariates to be selected as described below. The statistical model is defined as follows:

$$Y_{ijk} = (\alpha + a_i) + (\gamma + \beta_s T_k + g_i)\, t_{ij} + \beta_g\, Cov1_i + \beta_a\, Cov2_i + \varepsilon_{ij}$$

- Y_{ijk} is the value measured for ith patient at time j in treatment group k
- t_{ij} is the time of measurements for ith patient at study day j
- T_k =0 if patient in Placebo group and T_k=1 is patient in Pirfenidone
- β_s is the effect of Pirfenidone on the slope
- α and γ are elements of the intercept and slope respectively a_i and g_i are random specific components of the intercept and slope for the ith patient
- β_g , β_a are patient specific demographics' coefficients (strata)
- $Cov1_i$, $Cov2_i$ are covariates to be included for the ith patient
- ε_{ij} is the random error for ith patient at time j
- a_i and g_i are assumed to be normally distributed with mean 0 and arbitrary covariance matrix
- ε_{ij} are assumed to be independent and normally distributed with mean 0 and variance $\sigma\varepsilon^2$
- Within patient errors follow a random coefficient regression model with random effect for intercept and slope
- An unstructured variance-covariance structure will be used to model the within patient measurements
- The variance-covariance matrix, modeled to estimate the inter-individual variability is considered to have a Variance-Components structure

The model will be applied by adding the stratification factors MMF treatment and IPAF as covariates to the home spirometry data, once taking into account the old and once the new quality flag.

The same model with and without adding the stratification factors as covariates will be applied to the key secondary endpoint of site-measured FVC (mL).

4.5.7 Subgroup Analyses

Subgroup analyses will be conducted for the exploratory endpoint, as described in Section 4.5.4. The following subgroups will be based on:

- The four groups resulting from combinations of the two stratification factors:
    - Concomitant MMF treatment (yes/no)
    - Presence/absence of IPAF as defined by the MDT
- Gender: Male, Female
- Age (years): <65 years, ≥ 65 years
- Percent predicted FVC at Baseline: <65%, ≥65% to < 80%, ≥80%
- Percent predicted DLco at Baseline: <35%, ≥35%
- Body weight: <60 kg, ≥60 kg
- Previous Biopsy (yes/no)

4.5.8 Sensitivity Analyses for missing data

The robustness of the primary method of estimation described above will be explored by a series of sensitivity estimators based on varying assumptions underlying the multiple imputation strategy.

As the primary analysis for this study was performed in March 2019 the number of patients with missing FVC values at week 24 are known. No data was collected after treatment discontinuation.

3 different approaches will be used to evaluate the robustness of the analysis of the secondary endpoint to the missing at random (MAR) assumption.

Due to the low number, deaths and other intercurrent events have not been considered in the multiple imputation analysis.

4.5.8.1 Fixed missing imputation based on Placebo distribution

To evaluate the robustness of the analysis of the second endpoint to the missing at random (MAR) assumption missing data of both treatment groups will be imputed by descriptive statistics derived from the distribution of the placebo group. For each visit the following descriptive statistics of FVC (mL) will be calculated from the placebo group only: lower quartile, median, upper quartile.

For each of the 2 treatment groups 3 datasets with imputed missing values will be created:

- Missing values imputed by median of placebo group for the respective visit
- Missing values imputed by lower quartile of placebo group for the respective visit
- Missing values imputed by upper quartile of placebo group for the respective visit

Then, within each of the 9 possible combinations of datasets two analyses will be performed:

The mean FVC decline in the treatment arms will be compared using a student's t-test. The mean FVC decline for each treatment arm will be calculated using the estimated FVC decline for each individual patient, which will be obtained by applying a linear regression model to the data over time of the respective patient.

The decline in FVC (mL) at week 24 will be estimated from a random slope and intercept model. This model will include fixed effects for treatment, the stratifying variables concomitant use of MMF and presence/absence of IPAF and treatment-by time-interaction. Random effects will be included for both time and intercept.

The difference between treatment groups will be calculated together with the corresponding p-value.

A table will present the results from the two analyses: estimates for the placebo group, pirfenidone group and the comparison pirfenidone versus placebo together with the respective p-value for each of the 9 combinations of imputed values.

4.5.8.2 Fixed missing imputation between Q1 and Q3 of Placebo distribution

In another approach to evaluate the robustness of the analysis of the second endpoint to the missing at random (MAR) assumption a tipping point sensitivity analysis will be performed, where missing data of both treatment groups will be imputed by values derived from the range between lower and upper quartile (Q1 – Q3) in the Placebo group at each visit. The aim of the tipping point approach is to assess how severe departures from MAR could be in order to reverse conclusions from the analysis of secondary endpoint under different assumptions for the decline after withdrawal of the randomized treatment.

100 datasets with imputed values will be created for each treatment group. For the first dataset missing values in the respective treatment group will be imputed by the lower quartile (Q1) of placebo group within each visit. In the second dataset, the missing values will be imputed by Q1 plus the amount of 0.01 x (Q3 – Q1). The value added to Q1 will be increased within each subsequent dataset by another amount of 0.01 x (Q3-Q1), so that in the last of the 100 dataset the amount of Q3 from the placebo group will be imputed for missing values.

Then, for each of the 10000 combinations of datasets the decline in FVC (mL) at week 24 will be estimated from a random slope model This model will include fixed effects for the stratifying variables concomitant use of MMF and presence/absence of IPAF and treatment-by time-interaction. Random effects will be included for both time and intercept.

The difference between treatment groups will be calculated together with the respective p-value.

A heat map displaying positive and negative outcome based on the p-values for the comparison pirfenidone versus placebo with green and red colors (green: < 0.05, red: > 0.05) will be provided to illustrate the outcome of this analysis graphically. The robustness of the results will be discussed based on the magnitude of deviations from MAR required to change the results.

4.5.8.3 Tipping point analysis with shifts

An additional approach is to evaluate the robustness of the analysis of the secondary endpoint to the missing at random (MAR) assumption by performing a tipping point sensitivity analysis using the Multiple Delta Adjustment Method.

As a first step non-monotone missing data will be imputed 100 times using MCMC (Markov Chain Monte Carlo) to generate 100 data sets of longitudinal spirometry data (FVC [mL]) with monotone missingness pattern (PROC MI). Such a missingness pattern is the pre-requisite for subsequently applying sequential imputation and means that once a patient has a missing FVC value at a particular time point, FVC values at all subsequent time points also have missing values. The seed in PROC MI number will be set to 1234.

Once the monotone missing pattern has been created, the tipping point analysis for the longitudinal FVC data will be based on the Multiple Delta Adjustment Method. Data in each of the 100 generated datasets with the monotone missingness pattern will be imputed once by using sequential regression. A delta adjustment will be added to each imputed value. The value of each delta adjustment will be given by shift parameters S_1 and S_2 for the 2 treatments.

For patients with more than one monotone missing visit, multiple adjustments must be applied and since the imputation method is sequential, the effect of the adjustments is cumulative. S1 and S2 therefore represent the slope of a linear adjustment over time. This step will be repeated for a variety of combinations of S1 and S2.

For each combination of shift values S1 and S2 the 100 complete data sets will be analyzed using the statistical model as described above. The estimate of treatment difference at week 24 will be derived. Rubin's rules (16) will be used to combine the results from the analyses for each pair of S1 and S2 (PROC MIIANALYZE). Point estimates for the comparison pirfenidone versus placebo and respective p-values will be reported for selected combinations of S1 and S2 in a cross-table.

The following combinations of S1 and S2 will be applied:

• S1 (Pirfenidone): -130, -125,-120,-115,-110,-105,-100,-95,-90,-85,-80,-75,-70,-65,-60,-55,-50,-45,-40,-35,-30,-25,-20,-15,-10,-5,0, 5, 10

• S2 (Placebo): -40,-35,-30,-25,-20,-15,-10,-5,0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120.

A heat map displaying positive and negative outcome based on the p-values for the comparison pirfenidone versus placebo with green and red colors (green: < 0.05, red: > 0.05) will be provided to illustrate the outcome of this analysis graphically. The robustness of the results will be discussed based on the magnitude of deviations from MAR required to change the results (Rubin, 1987). Pharmacokinetic and Pharmacodynamic Analyses

No pharmacokinetic or pharmacodynamic analyses are planned for this study.

4.6 SAFETY ANALYSES

All safety analyses of data from the double-blind treatment period will be based on the safety population, i.e., the safety population will include all randomized patients who received at least one dose of trial treatment, with patients grouped according to treatment received. Safety data from the follow-up period will be summarized based on the safety follow-up population.

The safety objective for this trial is to evaluate the safety of pirfenidone vs. placebo.

No formal statistical testing will be performed for safety parameters.

Data collected during the 12-month safety follow-up will be analyzed separately (see section 4.7).

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 4.03, 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) version 20.1 or higher 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 modifications and treatment interruptions. Adverse events leading to treatment interruption or dose modification will also be summarized.

Laboratory parameters including hematology and the chemistry panel will be presented in shift tables of NCI-CTCAE version 4.03 grade at baseline vs. worst grade during treatment period. The laboratory parameters will be presented according to means, standard deviation, minimum, and maximum. Selected laboratory parameters will be also graphically presented over time. Liver abnormalities for the parameters total bilirubin, alkaline phosphatase, ALAT (SGPT) and ASAT (SGOT)) will be also presented.

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

4.6.1 Exposure of Study Medication

All analyses described in this section refer to the data collected in the drug-log for the double-blind randomized treatment period. Unknown doses will be excluded from the exposure analyses.

4.6.1.1 Treatment duration

Summaries of dosing, treatment duration, dose interruptions or reductions during the randomized double-blind treatment period will be provided for each treatment arm separately.

The overall treatment duration (weeks), including and excluding dose interruptions, will be summarized descriptively by treatment arm. The overall treatment duration including dose interruptions will be defined as follows:

[Date of last positive dose of randomized treatment received (pirfenidone/placebo) – date of first intake of randomized treatment) + 1)] / 7.

The overall treatment duration excluding dose interruptions will be derived from the treatment administration panels using the time windows described above, considering only days on treatment. i.e. positive dose.

Details on treatment administration, reductions or interruptions will be listed.

4.6.1.2 Doses and Dose modifications or interruptions

The total dose (mg), the average daily dose (mg/d) and the last dose administered (mg/d) will be presented descriptively for each of the study treatments.

The average daily dose will be calculated by summing up the number of capsules taken, divided by the overall treatment duration including dose interruptions as defined above.

Numbers and proportions of patients with at least one dose modification, or drug interruption, will be presented for each treatment arm separately. Numbers and proportions of patients with 1, 2, 3 or more dose modifications, or treatment interruptions, will be given.

The total number of dose modifications, reductions or treatment interruptions, will be presented together with numbers and frequencies of reasons for dose modification, reduction or treatment interruption.

Dose modifications, reductions or treatment interruptions will be presented as given in the drug logs dose strength and number of capsules taken.

In addition, dose intensity will be analyzed descriptively by treatment arm over time. For calculation of dose intensities, the time from first administration of randomized treatment to the end date of randomized treatment will be considered. The following formula will be used for calculation:

Dose intensity (DI) = (total dose received / total dose planned)*100.

4.6.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to a preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Agencies (MedDRA®). MedDRA version 20.1 or above and related SMQ lists will be used for coding.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. For AEs of varying severity, the most severe grade as documented on the eCRF will be used in the summaries. An AE will be considered severe if the most extreme grade will be larger or equal to 3.

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. All adverse events will be reported until 28 days after the last dose of study drug. After this period, the Investigator should report any SAEs that are believed to be related to prior study drug treatment.

For safety analysis of the double-blind treatment period treatment-emergent adverse events (TEAEs) will be defined as:

- AEs that started or worsened on or after first intake of randomized treatment until last positive dose of randomized treatment + 28 days

Adverse events that are reported after informed consent but before the first intake of randomized treatment will be considered as non-treatment-emergent AEs. These might include AEs that occur during the screening period.

Post-treatment AEs are not expected to occur, but will be defined as AEs that are reported more than 28 days after the last dose of randomized treatment for patients who do not enter the 12-month safety follow-up period. Those AEs will be listed.

The analysis of AEs within the framework of the primary study analysis will focus on treatment-emergent AEs (TEAE).

An overview of patient safety profile will present the number and proportion of patients in each treatment arm experiencing:

- Any and any related treatment-emergent adverse events (TEAE)
- Any and any related serious treatment-emergent adverse events (serious TEAE)
- Any and any related severe treatment-emergent adverse events (TEAEs ≥ Grade 3)
- Any and any related TEAE of special interest (AESI). 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: [ALT or AST >3 x ULN + total bilirubin >2 x ULN]

- Any and any related hepatic side effects: elevations in ALT and AST >3 × ULN at the same timepoint in the study.
- Any and any related gastrointestinal (GI) disorder (MedDRA SOC: GI Disorders)
- Any and any related photosensitivity (MedDRA Preferred terms Nodular rash, Photodermatosis, Photosensitivity reaction, Pruritus, Pruritus generalized). Potential updates in those terms will be needed in case the MedDRA version changes.
- Any and any related rash (MedDRA Preferred terms Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Solar dermatitis, Solar urticarial, , Sunburn, Erythema, Dry skin). Potential updates in those terms will be needed in case the MedDRA version changes.
- Angioedema (MedDRA preferred term Angioedema).
- Dizziness (MedDRA preferred term Dizziness).
- Fatigue (MedDRA preferred term Fatigue).
- Weight loss (MedDRA preferred term Weight loss).
- Increase 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.
- Any and any related TEAE leading to death
- Any and any related TEAE leading to treatment discontinuation

- Any grade 3-4 laboratory liver test results
    - ASAT (SGOT) results
    - ALAT (SGPT) results
    - alkaline phosphatase results
    - total bilirubin results

The incidence of TEAEs, related TEAEs, non-serious TEAEs, serious TEAEs, related serious TEAEs, grade 3-5 TEAEs and TEAEs leading to treatment discontinuation, dose modification or death will be summarized by treatment arm, by system organ class (SOC) and preferred term (PT) on the basis of the safety population. Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Additionally the total numbers of TEAEs will be provided for each SOC and overall.

Similar summary presentations will be provided for the incidence of TEAEs leading to dose reduction and drug interruption and TEAEs leading to hospitalization.

Non serious Treatment-emergent Adverse Events with >5% frequency will be also presented by SOC and PT. In addition, Serious Treatment-emergent Adverse Events, Fatal serious TEAEs and serious TEAEs related to pirfenidone or placebo will be presented in the same table by SOC and PT.

A summary table presenting the numbers and frequency of patients with TEAEs by most extreme CTCAE Grade (Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5) will be provided for each SOC and PT by treatment arm. In case the most extreme intensity is missing, it will be replaced by the initial intensity. If both most extreme and initial intensity are missing, the AE will be included in the Grade ≥3 category and a category for “missing” will be added.

Further, Kaplan-Meier curves for time to onset of first adverse event of the most relevant related TEAEs will be provided by treatment arm when the number of events are enough to do the analyses. These will include the following PTs or groups of AEs: Nausea, Diarrhoea, Weight decreased, Fatigue, Decreased appetite, and photosensitivity, or rash. In addition, the analysis will be done for the SOC GI.

All adverse event data will be listed by patient number and study day of onset including a flag variable for identifying the period of the event (double-blind treatment period or safety follow-up period). If the AE does not belong to any of the periods, the period flag will be missing.

In addition, for regulatory purpose two additional tables will be provided:

Frequency of adverse drug reactions occurring in patients treated with Esbriet (Pirfenidone) in clinical trials

TEAEs from day 1 of dosing until 168 days for MA39189 will be compared with the data from the phase III studies CAPACITY1 and 2 and ASCEND (restricted to first 168 days after first dose). The frequency of patients with related AEs (ADR) will be presented by System Organ Class and will be classified by their occurrences into

- Very common ((>=10% incidence rate)
- common ((>= 1% to <10% incidence rate)
- uncommon (>= 0.1% to <1% incidence rate)
- rare (>= 0.01% to <0.1% incidence rate)

Patients who withdrew from treatment during first 168 days of dosing will be censored at day of withdrawal for this analysis.

Rates of Adverse events per 100 patient years

TEAEs and SAEs from day 1 of dosing until 168 days for MA39189 will be compared with the data from the registrational phase III studies in IPF patients CAPACITY1 and 2 and ASCEND (restricted to first 168 days after first dose). The following parameters will be displayed in this analysis:

- duration of study in patient years (PY), calculated as sum of all patient's observation times).
- number of patients with at least one event,
- number of all events, defined as all AEs from all patients with onset date during observation time period
- rate of events per 100 PYs observation time, calculated as [number of events/duration] * 100
- 95% CI for this rate with
    - Lower limit = 100*[number of events – $z_{1-\alpha/2}$ * SQRT(number of events)]/duration
    - Upper limit = 100*[number of events + $z_{1-\alpha/2}$ * SQRT(number of events)]/duration

  where $z_{1-\alpha/2}$ is the 1-α/2 quantile of the standard normal distribution.

Patients who withdrew from treatment during first 168 days of dosing will be censored at day of withdrawal for this analysis. The analysis will be repeated for all TEAEs/SAEs from first day of dosing until 28 days of last dose, irrespective of the different study durations for MA39189 versus the phase III studies.

4.6.3 Deaths

Numbers and frequencies of deaths during double-blind period occurring until 28 days after the last dose of double-blind treatment will be presented by treatment arm. Deaths occurring more than 28 days after last dose for patients who did not enter the safety-follow-up period will also be presented separately.

All information associated with deaths collected in eCRF panel on study discontinuation will be listed. A flag variable will be included in the listing specifying the study period when the death occurred.

4.6.4 Laboratory Data

All of the laboratory tests will be conducted by the trial site's local laboratory.

All parameters will be graded according to NCI CTCAE (CTEP 2010), version 4.03, if applicable. Laboratory parameters that cannot be graded according to the corresponding NCI CTCAE version 4.03 will be assessed with respect to normal range (low, normal, high).

Laboratory parameters including hematology and the chemistry panel will be presented in shift tables of NCI-CTCAE version 4.03 grade at baseline versus worst grade during randomized double-blind treatment period. The laboratory parameters will be presented according to means, standard deviation, minimum, and maximum. Selected laboratory parameters will be also graphically presented over time.

The following laboratory 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).

Clinical laboratory values will be presented separately for CTCAE-gradable and non-CTCAE gradable parameters by laboratory panel (hematology, serum chemistry). For laboratory analyses, visits will be assigned to visit windows as described in Section 4.10. This will also be valid for possible unscheduled visits. In case that multiple evaluable assessments occur within the same visit, the nearest to midpoints value will be used for analyses.

The following summaries will be prepared:

For each laboratory parameter, descriptive statistics of laboratory values at each scheduled visit (derived as described above), and absolute changes from baseline to post-baseline will be presented by treatment arm.

Shift tables presenting categorical changes in CTCAE grade from baseline to worst grade recorded during the double-blind period, in the indicated direction, will be provided for CTCAE-gradable parameters by treatment arm. If no CTCAE grade is available for a specific laboratory variable, shift tables will present worst changes with respect to normal range category (low, normal, high).

Liver abnormalities (total bilirubin, alkaline phosphatase, ALAT (SGPT), ASAT (SGOT)) of Grade 3 and 4 will be presented showing numbers and percentages of patients for each parameter separately. Line graphs of liver parameters will be provided.

4.6.5 Vital Signs

Vital signs will include measurements of respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressures (mmHg) while the patient is in a seated position, temperature (C) and weight (kg). Vital signs will be assigned to visit windows as per Section 4.10. Descriptive statistics will be used to summarize vital signs data at baseline and at each scheduled post-baseline visit, and for the absolute change from baseline to each scheduled post-baseline visit by treatment arm during double-blind period.

4.6.6 ECG

Single ECG recordings will be obtained at specified time points, as outlined in the Schedule of Assessments (see Appendix 2), and may be obtained at unscheduled time points as indicated.

The following should be recorded in the appropriate eCRF: heart rate (beats/min), RR interval (msec), QRS interval (msec), PR duration (msec), uncorrected QT interval (msec), 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.

QTcF values of the safety population will be assigned to the following intervals: < 500 ms, 500–550 ms, and > 550 ms. Numbers and percentages of patients with their maximum QTcF interval category will be summarized by treatment arm over time. Absolute changes from the Baseline to each post-baseline visit in QTcF values will be categorized to < 31 ms, 31–60 ms, and > 60 ms. Numbers and percentages of patients in each category will be presented by treatment arm for each post-baseline visit or treatment discontinuation. Planned visits will be used for presentations.

Descriptive statistics for heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and the QTcF will be presented for each visit by treatment arm.

A listing containing ECG data will be presented.

4.7 SAFETY FOLLOW-UP ANALYSES

Data collected during the safety- follow-up period will be analyzed in the following way.

Adverse events during the 12-month safety follow-up period for pirfenidone treatment will be defined as:

- AEs that started or worsened on or after the date of safety follow-up period start until the end of the safety follow-up.

The safety follow-up population will be used for these analyses.

Summary tables for the incidence of AEs, related AEs, serious AEs, related serious AEs, severe AEs and severe related AEs will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Additionally, the total numbers of AEs will be provided for each SOC and overall. As with the end of the double-blind treatment period, an overview of safety will also be presented.

Pirfenidone exposure during safety-follow-up will be analyzed in a similar fashion as described in Section 4.7.1 with regard to treatment duration and amount of drug intake.

Data of laboratory assessments (AST, ALT, bilirubin, and alkaline phosphatase) and vital signs during safety-follow-up period will be analyzed in a similar fashion as described in Section 4.7.4 and Section 4.7.5 .

Data will be presented by randomized treatment labeled as 'Randomized Pirfenidone' and 'Randomized Placebo'.

4.8 MISSING DATA

With exception of the tipping point analysis described in section 4.5.8, missing data will not be imputed. Other exceptions will be made for the data related to adverse events and concomitant medications as described below.

For adverse events, missing start dates will only be imputed for determination of whether the adverse event is considered to be treatment-emergent or not.

Incomplete or missing onset dates will be imputed to the earliest date possible (using any reliable portions of the onset date that are available). The onset day is considered unreliable if the month or year portions of the date are missing.

In case the month portion of the AE start date is missing, the AE start date will be imputed to the earliest day possible by using the following principles:

- If Treatment Start Date is missing, then the AE Start Date will be imputed as 01-01-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

- When the Treatment Start Date is not missing, and the years of AE Start Date and Treatment Start Date coincide, the AE onset date will be set to the Treatment Start Date

- When the Treatment Start Date is not missing, and the years of the AE Start Date and the Treatment Start Date do not coincide, then the AE Start Date will be imputed as 01-01-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

In case the day portion of the AE Start Date is missing, the AE Start Date will be imputed to the earliest day possible as follows:

- If the Treatment Start Date is missing, then the AE Start Date will be imputed as 01-MMM-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

- When the treatment date is not missing, and the years and months from the AE Start Date and the Treatment Start Date coincide, the AE onset date will be set to the Treatment Start Date

- When the Treatment Start Date is not missing, and AE Start Date is after the Treatment Start Date according to the given year or month, then the AE Start Date will be imputed as 01-MMM-YYYY

If the AE stop date is missing, then the event will be assumed to be ongoing and a stop date will not be imputed.

In the case the treatment end date is missing and it cannot be judged whether the event occurred during the period of Treatment Start Date to Treatment End Date plus 28 days, the AE will be considered treatment-emergent as long as it is not flagged as prior AE.

For imputation and handling of missing intensity or relationship to study medication, please see Section 4.7.2.

All other missing or incomplete adverse event data will be left as missing.

For concomitant medications, missing start or end dates will only be imputed to determine whether the medication is considered to be prior, on-treatment, post-treatment.

In general if only the day is missing from the start date then the missing day will be imputed as 01-MMM-YYYY unless the month is the same month as the start of study medication in which case the missing date will be imputed as the treatment start date.

If both the day and month are missing from the start date then the start date will be imputed as 01-JAN-YYYY.

If both the day and month are missing from the start date year is the same as treatment start date then the start date will be imputed as ‘treatment start date’, but if the year is after treatment start date, the start date will be imputed as 01-JAN-YYYY.

If the day, month and year are all missing from the start date then the start date will be imputed as 01-JAN for the year in which the patient was recruited to the study.

If the day, month and year are all missing from the start date then the start date will be imputed as ‘treatment start date’.

If an incomplete stop date has both the year and month present, the day will be imputed as the last day of the month or date of discontinuation/death.

If the AE is ongoing at time of primary analysis, concomitant medication will be summarized for the double-blind treatment period and safety follow-up.

4.9 VISIT WINDOWS

Visit windows for double-blind treatment period will be applied to vital signs and laboratory data and the derived visits will be used in the by-visit summarizations. If multiple observations fall within the same visit window, the observation with the nearest to midpoint value will be used in the analysis, if not stated otherwise. If subjects discontinue from the double-blind treatment period early the data will be assigned to the early discontinuation visit. The date of early discontinuation will be considered as the target date.

The “Baseline” visit is a derived data point to identify baseline values which are used to calculate the change from baseline values. Baseline is defined in Section 4.2.2.

The End of Treatment [EOT] visit will either be a copy of early discontinuation records for patients who prematurely discontinued double-blind treatment period or Week 24 records for patients who completed the double-blind treatment period.

Table 2 Visit Windows

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	1	Last valid assessment prior to first intake of randomized study drug (pirfenidone/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (pirfenidone/placebo) was given.
Week 4 [4]	28	One day after first dose of randomized treatment to 42
Week 8 [8]	56	43 to 70
Week 12 [12]	84	71 to 98
Week 16 [16]	112	99 to 126
Week 20 [20]	140	127 to 154
Week 24 [24]	168	155 to a maximum of 195 if the patient did not early discontinued.

Early discontinuation [25]	Not applicable	As occurred
End of treatment (EOT) [26]	Not applicable	As occurred
Follow-up visit (FUP1) [27]	Not applicable	As occurred
Safety follow-up visits(SFUP) [28]	Not applicable	As occurred: Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months
Additional Safety follow-up visit [29]	Not applicable	As occurred: up to 12 months plus 28 days

4.10 INTERIM ANALYSES

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.

No formal interim analyses for efficacy are planned.

4.11 BIOMARKER ANALYSES

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 2).

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.

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

Analyses on biomarker data will not be in the scope of this SAP, but will be planned and described separately.

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Appendix 1
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 Appendix 3 PRO Questionnaires

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 of the CSP) 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. 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. 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. A Follow-up Visit will occur 28 days after the end of the 24-week double-blind treatment period.

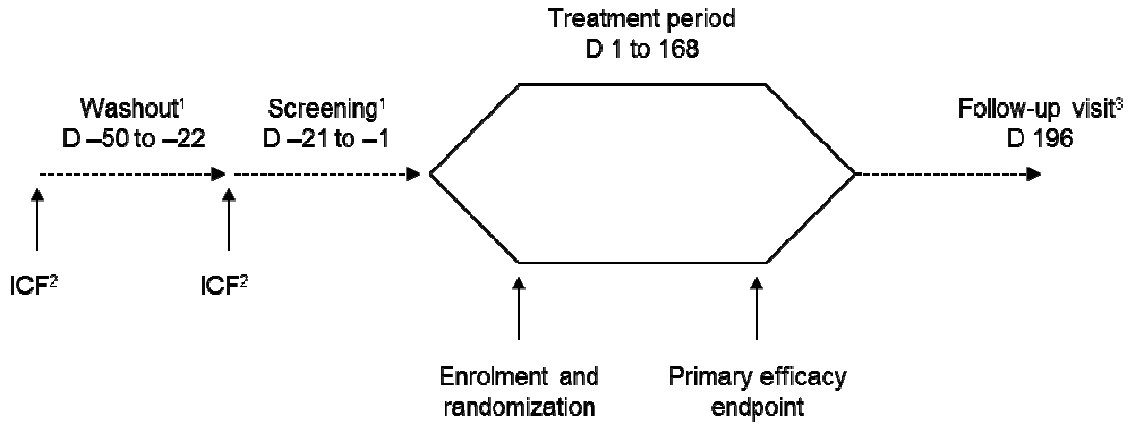
After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the safety follow up period, the patients 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 Appendix 3 PRO Questionnaires below.

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 2). 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.

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.

Appendix 2 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												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	

	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												Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
Weight		x							x	x			
Height		x											
Complete physical examination [g]		x	x						x	x			
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	

	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												Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
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			

	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												Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
UCSD-SOBQ [q]			x			x			x	x			
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			

	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												Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months	
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.

[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. 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.

a.

Appendix 3 PRO Questionnaires

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	None of the time

					time	
13. In the last 2 weeks, my cough has made me feel fed up						
1 All of the time	2 Most of the time	3 A lot of the time	4 Some of the time	5 A little of the time	6 Hardly any of the time	7 None of the time
14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?						
1 All of the time	2 Most of the time	3 A lot of the time	4 Some of the time	5 A little of the time	6 Hardly any of the time	7 None of the time
15. In the last 2 weeks, have you had a lot of energy?						
1 None of the time	2 Hardly any of the time	3 A little of the time	4 Some of the time	5 A lot of the time	6 Most of the time	7 All of the time
16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?						
1 All of the time	2 Most of the time	3 A lot of the time	4 Some of the time	5 A little of the time	6 Hardly any of the time	7 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 All of the time	2 Most of the time	3 A lot of the time	4 Some of the time	5 A little of the time	6 Hardly any of the time	7 None of the time
18. In the last 2 weeks, my cough has interrupted conversations or telephone calls						
1 Every time	2 Most times	3 A lot of the time	4 Some of the time	5 A little of the time	6 Hardly any of the time	7 None of the time
19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends						
1 Every time I cough	2 Most times when I cough	3 Several times when I cough	4 Sometimes when I cough	5 Occasionally when I cough	6 Rarely	7 Never
Thank you for completing this questionnaire.						

Scoring

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.

The scores from each of the following questions are added together to provide the mean score for each domain:

1. Physical: 1, 2, 3, 9, 10, 11, 14, 15
2. Psychological: 4, 5, 6, 12, 13, 16, 17
3. Social: 7, 8, 18, 19

Domain scores: total score from items in domain/number of items in domain (range 1–7).

Total scores: addition of domain scores (range 3–21).

UCSD-SOBQ

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

Scoring

Twenty one items assess the severity of shortness of breath during specific activities associated with daily living if patients do not routinely perform the activity, they are asked to estimate the degree of shortness of breath anticipated. Three additional items ask about limitations due to: shortness of breath, fear of harm from overexertion and fear of shortness of breath.

Each of the 24 activities are rated on how dyspnea affects the activity on a 6-point scale:

0 = None at all to 5 = Maximal or unable to do because of breathlessness

The scores from all 24 questions are totalled to provide a score in the range 0 – 120.

SGRQ

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
☐	☐	☐	☐	☐

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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 ☐

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 these days.

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	☐	☐

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	☐	☐

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.

STRUCTURE OF SGRQ

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in patients with diseases of airways obstruction.

Part 1 (Questions 1-8) addresses the frequency of respiratory symptoms. It is not designed to be a precise epidemiological tool, but to assess the patient's perception of their recent respiratory problems.

Part 2 (Sections 9-16) addresses the patient's current state (i.e. how they are these days).

The Activity score measures disturbances to daily physical activity. The Impacts score covers a range of disturbances of psycho-social function. Validation studies for the original SGRQ showed that this component relates in part to respiratory symptoms, but it also correlates quite

strongly with exercise performance (6-minute walk test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

Three component scores are calculated for the SGRQ

Symptoms – concerned with the effect of respiratory symptoms their frequency and severity

Activity concerned with activities that cause or are limited by breathlessness

Impacts covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease.

Total score summaries the impact of disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

SGRQ SCORES IN HEALTHY SUBJECTS

Means (95% confidence intervals) for SGRQ scores in normal subjects with no history of respiratory disease

N	Age-years	FEV1 as % predicted	Symptoms score	Activity score	Impacts Score	Total Score
72	46 (17 - 80)	95 (91-99)	12 (9-15)	9 (7-12)	2 (1-3)	6 (5-7)

Scoring

Questions 1 – 7 The eCRF screens should be set up so that where a patient has ticked a box, a value of 1 is entered for the appropriate question. By default, the empty boxes are entered as 0. Where a patient has missed a question the cells on the spreadsheet are left blank. Example: Response = 1c, 'Over the last year I have coughed a few days a month'. A value of 1 is entered for 1c and a value of 0 is entered for 1a, 1b, 1d and 1e. If no tick was present for question 1 then 1a to 1e would be left blank.

Question 8 Where a patient has ticked 'Yes' to having a worse wheeze in the morning, a value of 1 is entered for the appropriate question. All other responses are entered as 0. Example: Do you have a wheeze? = 'Yes' and Worse in the morning = 'Yes'. then response to question 8 = 1. Do you have a wheeze? = 'Yes' and Worse in the morning = 'No'. Or, Do you have a wheeze? = 'No'. then response to question 8=0.

Questions 9, 10 & 17 Where a patient has ticked a box, a value of 1 is entered for the appropriate question. The empty boxes are entered as 0. Where a patient has missed the question the cells on the spreadsheet are left blank. Example: Response = 10a, 'My chest trouble made me stop work'. A value of 1 is entered for 10a and a value of 0 is entered for 10b and 10c. If no tick was present for question 10, then 10a to 10c would be left blank.

Questions 11 – 16 Where a patient has ticked 'True' a value of 1 is entered for the appropriate question and where a patient has ticked 'False' a value of 0 is entered. Where a patient has missed a question the cell on the spreadsheet is left blank.

Example: 15a = 'True' then 15a = 1.

14c = 'False' then 14c = 0.

13h = missing then 13h is left blank

In response to question 14, if a patient is not receiving medication, enter the responses as zero, otherwise the calculator will read the values as missing.

Missing Questions

There should not be any missing items in the questionnaire, but the SGRQ can have up to 24% of missing items in the questionnaire. If more than 24% of items are missing the scores will be missing.

ITEM WEIGHTS

Once the questions have been answered the following weights are applied to the individual responses

PART 1

Over the past 3 months, I have coughed:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
80.6	63.2	29.3	28.1	0.0

Over the past 3 months, I have brought up phlegm (sputum):

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
76.8	60.0	34.0	30.2	0.0

3) Over the past 3 months, I have had shortness of breath:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
87.2	71.4	43.7	35.7	0.0

4) Over the past 3 months, I have had attacks of wheezing:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
86.2	71.40	45.6	36.4	0.0

5) During the past 3 months, how many severe or very bad unpleasant attacks of chest trouble have you had?

More than three	3 attacks	2 attacks	1 attack	None
86.7	73.5	60.3	44.2	0.0

6) How long did the worst attack of chest trouble last?

a week or more	3 or more days	1 or 2 days	Less than a day	None
89.7	73.5	58.8	41.9	0.0

7) Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

No good days	1 or 2 good days	3 or 4 good days	Nearly every day	Every day
93.3	76.6	61.5	15.4	0.0

8) If you have a wheeze, is it worse in the morning?

No	Yes
0.0	62.0

PART 2

The weights in Part 2 are also applied to the individual responses to each question. The worse the impact the higher the weight. This means that weights are not applied sequentially in the order that the response is given.

9) How would you describe your chest condition?

The most important problem I have	83 .2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0

10) If you have ever had paid employment?

My chest trouble made me stop work	88.9

My chest trouble interferes with my work or made me change my work	77.6
My chest trouble does not affect my work	0.0

11) Questions about what activities usually make you feel breathless.

Sitting or lying still	90.6
Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or games	72.1

12) More questions about your cough and breathlessness.

My cough hurts	81.1
My cough makes me tired	79.1
I get breathless when I talk	84.5
I get breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84.0

13) Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I do not expect my chest to get any better	82.3
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5

14) Questions about your medication.

My medication does not help me very much	88.2

I get embarrassed using my medication in public	53.9
I have unpleasant side effects from my medication	81.1
My medication interferes with my life a lot	70.3

15) Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81.0
I walk more slowly than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle,swim fast or play competitive sports	63.5

16) We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do housework	79.1
I cannot move far from my bed or chair	94.0

17) Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do	0.0
It stops me doing one or two things I would like to do	42.0
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

SCORING ALGORITHM

Three component scores are calculated: **Symptoms; Activity; Impacts**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive response are summed.

ii The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.

iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

Score = 100 x Summed weights from positive items in that component

Sum of weights for all items in that component

The Total score is calculated in similar way:

Score = 100 x Summed weights from positive items in the questionnaire

Sum of weights for all items in the questionnaire

Sum of maximum possible weights for each component and Total:

Symptoms 662.5

Activity 1209.1

Impacts 2117.8

Total 3989.4

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient).

It will be noted that the questionnaire requests a single response to questions 1-7, 9-10 and 17. If multiple responses are given to one of these questions then averaging the weights for the positive responses for that question are acceptable

SYMPTOMS COMPONENT

This is calculated from the summed weights for the positive responses to questions 1-8.

ACTIVITY COMPONENT

This is calculated from the summed weights for the positive responses to questions 11 and 15.

IMPACTS COMPONENT

This is calculated from the summed weights for the positive responses to questions 9-10, 12- 14 and 16-17.

TOTAL SCORE

The Total score is calculated by summing all positive responses in the questionnaire and

expressing the result as a percentage of the total weight for the questionnaire

HANDLING MISSED ITEMS

There should not be any missed items but if there are missing items the scores should be calculated using the following rules:

following should be used: The following method is recommended for missing items:

Symptoms

The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4).

Activity

The Activity component will tolerate a maximum of 4 missed items. The weight for the

missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4).

Impacts

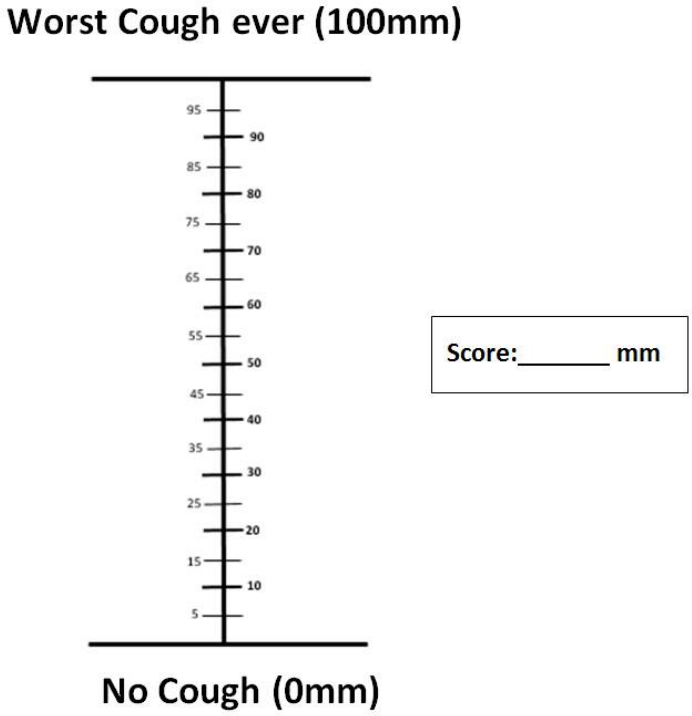
The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4).

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.

Cough Visual Analogue Scale (VAS)

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.



Score:_____ mm

STATISTICAL ANALYSIS PLAN

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**
STUDY DRUG:	**Pirfenidone (RO0220912)**
VERSION NUMBER:	**Version 2.0 Final 29-Oct-2018**
IND NUMBER:	**67284**
Eudract Number:	**2016-002744-17**
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted]; [redacted] (F. Hoffmann-La Roche Ltd)
DATE FINAL:	29 October 2018

SIGNATURE PAGE

Roche Biostatistician [redacted] [redacted]

30-Oct 2018

Date

Study Biostatistician [redacted] [redacted]

31-OCT-2018

Date

[redacted] [redacted] [redacted]

30-Oct-2018

Date

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The following changes were made compared to the first version of the SAP:

Version	Date	Change number	Change description
2	08-Oct-2018	1	Clarification related to the aim and timeline of the primary analysis and final analysis of the study are included under section Outcome Measures.
2	08-Oct-2018	2	Week 28 is included in all descriptive efficacy tables.
2	08-Oct-2018	3	The safety follow-up period definition is changed as stated in section On-treatment Assessments (12-Month Safety Follow-up Period).
2	08-Oct-2018	4	Disposition is updated in section Patient Disposition.
2	08-Oct-2018	5	Details were added in order to analyze valid daily spirometry data in section Demographic and Baseline Characteristics.
2	08-Oct-2018	6	Additional analyses needed in the safety follow-up period based on safety follow-up population are presented under section Safety Follow-up analyses.
2	08-Oct-2018	7	Safety follow-up visits were included under section Visit Windows.
2	08-Oct-2018	8	Listings of stratification factors, separated types of adverse events and pregnancy data were removed from the corresponding sections.
2	29-Oct-2018	9	Post-medications during safety follow-up period are adapted as per new period definition in section Previous and Concomitant Medication.

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LIST OF ABBREVIATIONS

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
BP	blood pressure
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
CSP	clinical study protocol
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
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
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
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 mycophenolate acid
NAC	N-acetyl-cysteine
NCI	National Cancer Institute
NGS	next-generation sequencing
NSIP	nonspecific interstitial pneumonia
PDGF	platelet-derived growth factor
PDMS	protocol deviation management system
PFS	progression-free survival
PFTs	pulmonary function tests
PRO	patient-reported outcome
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cells
RBR	Research Biosample Repository
RNA	ribonucleic acid
RoW	Rest of the World
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SGRQ	St. George's Respiratory Questionnaire
SOBQ	Shortness of Breath Questionnaire
SOC	System Organ Class
SOP	standard operating procedure
SpO2	oxyhemoglobin saturation at rest

SSc	systemic sclerosis
TGF	transforming growth factor
TID	three times daily
UCSD	University of California, San Diego
UIP	usual interstitial pneumonia
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale
VC	vital capacity
WBC	white blood cells
WGS	whole genome sequencing

1. BACKGROUND

As described in the Clinical Study Protocol (CSP) Section 1.3, no approved treatments are available for the 15% of patients with interstitial lung disease (ILD) who have unclassifiable disease. 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 idiopathic pulmonary fibrosis (IPF) are sufficiently encouraging 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 (Esbriet®) 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.

Mycophenolate mofetil/sodium or mycophenolic acid (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. 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. STUDY DESIGN

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 multidisciplinary team (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.

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.

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 CSP) 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 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. 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 CSP 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. 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, patients will be given the opportunity to receive open-label pirfenidone within a safety follow-up period of up to 12 months of the 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. 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.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1 and the Schedule of Assessments in Appendix 2 For additional details, please see the CSP Version 3, 28 June 2018 (and its Appendices).

2.2 OUTCOME MEASURES

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).

The primary analysis of the primary and secondary efficacy outcome measures of this study is planned to be performed when the last patient reached the date of the last follow-up visit after end of the double-blind treatment period.

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy objective for this trial is to evaluate the effect of pirfenidone vs. placebo on lung function parameters on the basis of Forced Vital Capacity (FVC) measurements. FVC will be measured daily by the patients by use of a handheld spirometer.

The primary efficacy endpoint is defined as:

- rate of decline in FVC in mL measured by daily handheld spirometry over the 24-week double-blind treatment period.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy objective for this trial is to evaluate the efficacy of pirfenidone compared with placebo from baseline until Week 24 on other functional parameters, outcomes, and patient reported outcomes (PROs).

The following endpoints will be analyzed:

- 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 diffusing capacity of the lung for carbon monoxide (DLco)
- Change in (6-minute walk distance) 6MWD in meters
- Change in University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) score
- Change in score in Leicester Cough Questionnaire
- Change in cough visual analog scale
- Change in total and sub-scores of the St. George's Respiratory Questionnaire (SGRQ)
- Non-elective hospitalization, both respiratory and all cause
- Incidence of, and time to first, investigator-reported acute exacerbations
- Progression free survival (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

2.2.3 Exploratory Efficacy Outcome Measures

One exploratory objective for this trial is to evaluate the role of mycophenolate mofetil/sodium or mycophenolic acid (MMF) treatment in ILD and to evaluate potential biomarkers associated with fibrosis and ILD.

The exploratory endpoints associated are:

- Efficacy and safety data from subgroups of patients who did or did not receive MMF treatment
- Biomarker data from plasma, serum, and whole blood ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) samples

2.2.4 Safety Outcome Measures

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

- 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

All analyses with regard to the safety outcome measures will be performed from the date of first randomized treatment intake until 28 days after the last positive dose during the double-blind randomized treatment period.

2.3 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.

2.4 INTERIM ANALYSIS

There are no planned interim efficacy analyses for this trial.

3. STUDY CONDUCT

The study conduct is described in Section 2.

3.1 RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURES

Patients will be randomized 1:1 to receive either pirfenidone or 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 arm, 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 CSP 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.

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review safety data and advice on study conduct at least three times during the study. Efficacy data will only be provided if requested by the iDMC. A first meeting is planned 6 months after start of recruitment,

and subsequently at 12 and 18 months. Details on procedures and safety review by the iDMC are described within an iDMC charter.

4. STATISTICAL METHODS

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate). Percentages will be based on the number of patients in each treatment arm for the analysis population, if not otherwise specified.

Continuous endpoints will be summarized using descriptive statistics (mean, standard deviation, minimum, 25th and 75th quartiles, median, and maximum).

Where data will be summarized over time, the following timepoints will be presented as applicable: Baseline, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28 (if applicable) and early discontinuation visit.

Data analysis of data collected during the 12-month safety follow-up period will be described in section 4.8.

Where applicable other analysis methods will be specified below.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-treat Population

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in the ITT population will be assigned to treatment arm as randomized (planned treatment). The ITT population is the primary analysis population for all efficacy analyses. The time period for all efficacy analyses is defined from date of randomization until the treatment completion date of the double-blind treatment period or the date of early discontinuation collected on the early treatment discontinuation eCRF page in case a patient does not complete the planned 24 weeks of double-blind treatment.

4.1.2 Per Protocol Population

Not applicable.

4.1.3 Safety Population

The safety population is defined as all patients with at least one intake of pirfenidone or placebo, i.e. at least one record in the drug-log of the double-blind period with a non-zero dose.. Patients in the safety population will be assigned to treatment arm according to the actual treatment they received.

4.1.4 Safety Follow-up Population

For the 12-month safety follow-up period, the safety follow-up population will be defined as all patients who have received at least one dose of pirfenidone after the randomized treatment end plus 28 days.

Safety analyses for the 12-month follow-up period will be performed from the date of the first pirfenidone drug intake during safety follow-up period up to the study completion/discontinuation visit.

4.2 TRIAL PERIODS, OBSERVATION AND ANALYSIS TIMES

Where durations are to be calculated (e.g. treatment duration), these will be derived based on the interval in days (end date – start date + 1) and converted to months and years if needed, using 30.4375 and 365.25, respectively, as denominator if not otherwise specified.

For the investigational medicinal product (IMP) exposure, treatments administered from the date of first randomized pirfenidone/placebo treatment up to the date of completion of double-blind treatment or date of early treatment discontinuation, will be regarded.

For drug safety, analyses will be restricted to AEs or assessments that occurred from the first day of randomized treatment until the date of last positive dose of randomized treatment plus 28 days.

Safety analyses for the 12-month follow-up period will be performed using the time window from the safety follow-up period start up to the study completion/discontinuation visit.

4.2.1 Study Days

Study days will be defined as the number of days since randomization, and is calculated as:

- Study day = Assessment date – randomization date + 1, for assessments on or after the randomization date.
- Study day = Assessment date – randomization date, for assessments before the randomization date.

The day of randomization will be study day 1.

4.2.2 Baseline and Screening Observations

Table 1 Definition of Baseline and Screening Observations

	Definition
Baseline data	Baseline is defined as the last valid assessment prior to first intake of randomized study drug (pirfenidone/placebo). This may not be the same as the Day 1 (Week 1) visit as per eCRF. In case that Day 1 (Week 1) visit data is missing and the randomized

	treatment is given, data from the screening period will be used as baseline. In addition, if randomized treatment is not given then baseline will be defined as the last valid assessment collected either screening or day 1. Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (pirfenidone/placebo) was given. Adverse events occurring on the date of first randomized pirfenidone/placebo treatment will not be considered baseline, but treatment-emergent.
Screening data	Screening measurements are all the measurements performed before the randomization date.

4.2.3 On-treatment Assessments for Efficacy Analyses (Double-blind Treatment Period)

For efficacy analyses, on-treatment assessments will be the assessments performed on or after the randomization date until the double-blind treatment completion or discontinuation date.

4.2.4 On-treatment Assessments for Safety Analyses (Double-blind Treatment Period)

For safety analyses, on-treatment assessments will be the assessments performed on or after the first dose of randomized pirfenidone/placebo date until the last positive dose of randomized treatment plus 28 days.

4.2.5 On-treatment Assessments (12-Month Safety Follow-up Period)

Details of all data recorded during the 12-month safety follow-up period will be presented. This period starts on the day of the first positive dose of pirfenidone on or after the 28 days follow-up visit for patients who completed the double-blind treatment period without being discontinued the study. The safety follow-up period ends with the study completion/discontinuation visit, with a maximum duration of 12 months plus 28 days. Safety follow-up analyses will be presented separately from double-blind treatment phase ones.

4.2.6 Cut-off points

The clinical cut-off for the primary analysis will occur when the last patient has completed the final safety Follow-up Visit, 28 days after the double-blind treatment period.

There will be a second cut-off for the final analysis when all patients have completed the 12-month safety follow-up 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) plus 28 days and a final safety Follow-up Visit 4 weeks after the last dose.

4.3 ANALYSIS OF TREATMENT ARM COMPARABILITY

To ensure the comparability of the treatment arm, the randomization will be stratified by the availability of a previous MMF treatment (yes/no) and the presence/absence of IPAF as defined by MDT to ensure an equal distribution of patients.

These stratification factors will be included in the analysis of the primary endpoint as a sensitivity analysis. Please refer to the corresponding section 4.4.5 for further details.

Outputs for concordance between the stratification factors by eCRF and by IxRS will also be presented.

4.4 ANALYSIS OF STUDY CONDUCT

Unless otherwise specified, all analyses described in this section will be performed on the ITT population, presenting data by treatment arm.

4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients enrolled, screened, failed screening, randomized, treated, completed or early discontinued the double-blind treatment period, patients entering the 12-month safety follow-up period and their current status (ongoing, completion, discontinued) in that period will be provided. For patients who have early discontinued the double-blind treatment period or the study, frequencies of reasons for early discontinuation will be provided. A listing with all the patient disposition data will be also presented.

The following definitions will be used:

- Patients randomized: All patients who have been randomized to receive either pirfenidone or placebo, i.e. have a randomization date.
- Patients randomized and not treated: all randomized patients who have not received at least one dose of the randomized treatment.
- Patients randomized and treated: all randomized patients who have received at least one dose of the randomized treatment.
- Patients randomized and treated with sufficient post-baseline efficacy data: all randomized patients who have received at least one dose of the randomized treatment and have at least one post-baseline assessment of FVC (mL).

- Completion of double-blind treatment period: eCRF question “Did the patient complete course of double-blind treatment?” is ticked “Yes” (eCRF form “Double-blind treatment Completion/Early Discontinuation”).

- Early discontinuation (non-completion) of double-blind treatment period: eCRF question “Did the patient complete course of double-blind treatment?” is ticked “No” (eCRF form “Double-blind treatment Completion/Early Discontinuation”).

- Early discontinuation (non-completion) of study: eCRF question “Did the subject early discountinue from the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”) for patients who discontinued double-blind treatment period.

- Early discontinuation (non-completion) of study: eCRF question “Did the subject early discountinue from the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”) for patients who completed double-blind treatment period and did not enter 12-month safety follow-up period.

- Status during the 12-month safety follow-up (entered, ongoing, completed). Completers are defined as those patients that have filled the study completion/discontinuation form. Otherwise, the patient is considered ongoing in the safety follow-up phase.

- Completion of study: eCRF question “Did the subject complete the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”)

- Early discontinuation (non-completion) of study: eCRF question “Did the subject early discountinue from the study?” is ticked “Yes” (eCRF form “Study Completion/Early Discontinuation”)

An overview on patients’ enrolment will be provided based on the randomized subjects by country and center separately for the pirfenidone and placebo arm.

Kaplan-Meier (KM) plots for time to treatment discontinuation will be provided for all randomized patients and by randomized arm, based on the date subject completed or early discontinued from double-blind treatment period, as per eCRF. If the patient completed the treatment without treatment discontinuation, then it will be censored to the date of treatment completion.

In addition, KM plots for time to study discontinuation will be presented for all randomized patients by arm, based on the study discontinuation date. If the patient completed the study as planned per protocol, then the patient will be censored to the study completion date.

In addition, a consort diagram with some of the categories above will be presented.

4.4.2 Major Protocol Deviations

Major protocol deviations and eligibility violations will be summarized by frequency tables and all patients with protocol deviations will be listed. Protocol deviations will be collected in the protocol deviation management system (PDMS), reviewed by the medical monitors, and will be provided in a SAS dataset via the Biometrics Computing Environment (BCE). All deviations provided in that dataset will be considered as major protocol deviations.

4.4.3 Demographic and Baseline Characteristics

Baseline and disease characteristics such as demographics, medical history and tobacco use history will be summarized by descriptive statistics or frequency tables for each treatment arm.

Demographics

The following demographic characteristics will be summarized by treatment arm:

- Age (years): as entered in the eCRF at the screening visit.
- Age categories: <65, and ≥ 65.
- Age categories: <45, ≥45 to <65 years, ≥65 to <85 years, and ≥ 85 years.
- Gender: Male/Female.
- Race: White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Unknown. In case that more than one race will be ticked, a concatenated variable, containing all races will be presented (e.g. Asian/White).
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown.
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m2) at baseline. BMI will be calculated as: weight(kg) / (height(m))2
- Female reproductive status: childbearing potential without contraceptive protection, Childbearing potential with contraceptive protection, surgically sterilized, Postmenopausal, Pre-menarchal, Non childbearing potential.

Data on female reproductive status will be presented descriptively.

Demographic data will be also listed.

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 20.1 or higher and will be summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT) by treatment arm. If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

A listing with past and ongoing medical history data from the washout period will be presented.

Tobacco use history

The history of tobacco use will be summarized by treatment arm with the following characteristics:

- Tobacco use history (never, current, previous)
- Nicotine exposure (pack-years), smokers only

Numbers and percentages of patients will be provided for tobacco use history. Nicotine exposure will be summarized descriptively.

Diagnosis and time from uILD Diagnosis

Frequencies and percentages will be presented for the uILD category collected into the eCRF page MDT/Diagnosis (Eligibility).

The time in months since the original uILD diagnosis will be calculated as

Date of randomization – Date of ILD diagnosis and will be summarized descriptively by randomized treatment arm. The number and percentage of patients with a historical high-resolution computed tomography and with a historical surgical lung biopsy will also be presented.

Descriptive statistics of the time from most recent historical high-resolution computed tomography (months) and historical surgical lung biopsy will be presented. As above, the date of randomization will be used as reference date for calculation of duration.

Stratification Factors

The number and percentage of patients that fall into each of the four groups based on the two stratification factors: Concomitant MMF treatment (yes/no), and the presence/absence of IPAF as defined by the MDT will be presented by treatment arm.

Baseline Spirometry Test

The values recorded for the baseline assessments of the spirometry tests were the following:

- Forced vital capacity (FVC) (L and % predicted)
- Forced expiratory volume in 1 second (FEV1) (L and % predicted)
- FEV1 (L) / FVC (L) ratio (1)
- Carbon monoxide diffusing capacity (DLco) (% predicted)

Descriptive statistics will be provided for these parameters separately for treatment arm.

Historical Spirometry Test

The number and percentage of patients who performed spirometry test (FVC, DLco, FEV1, and FEV1/FVC ratio) in the past will be provided. The most recent assessment before the Screening visit will be collected:

- Hemoglobin corrected DLco (mmol/min/kPa and %)
- DLco/Va (KCO) (mL/min/mmHg/L and % predicted)
- FVC (L and % predicted)
- FEV1 (L and % predicted)
- FEV1(L)/FVC(L) ratio (1)

These historical spirometry test parameters will be summarized using descriptive statistics by treatment arm. Both, absolute and percent predicted values will be presented. Frequencies and percentages will be presented for the high-resolution computed tomography and the surgical lung biopsy.

Baseline Daily Spirometry (Handheld Device) and Site Spirometry

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. The following blow categories will be collected:

Not acceptable maneuvers	Acceptable maneuvers
• **Rejected** • **Borderline Accepted**	• **Accepted**

Only acceptable maneuvers will be considered for the analysis. If one patient has more than one accepted measurement per day, all of them will be used for the analysis.

FVC (mL) will be measured daily with a handheld device.

Descriptive statistics of the baseline site measurements will be provided for these parameters separately by treatment arm together with the efficacy results.

Baseline 6-minute walk distance (6MWD)

The 6MWD is used to evaluate the functional capacity of patients with lung disease. The 6MWD measures the distance a patient is able to walk quickly on a flat, hard surface in a period of 6 minutes.

The number and percentage of patients that

- Performed the 6-minute walking test (yes/no),
- Rested for at least 10 minutes (yes/no),
- Stopped the test before 6 minutes (yes/no),
- Required O2 (yes/no)

at the baseline visit will be summarized by randomized treatment group.

The values of the parameters recorded for the 6MWD test are:

- Vital signs (Heart rate (beats/min), systolic blood pressure (mmHg), diastolic pressure (mmHg)) (before the test, at the end of the test)
- Distance walked (m),
- Oxyhemoglobin saturation (SPO2) (before the test (at rest), at the end of the test),
- Oxygen (O2) requirements (L) (at the end of the test)

will be summarized descriptively by treatment arm.

4.4.4 Previous and Concomitant Medication

Previous and concomitant medications will be presented based on the safety population. Post medications administrated during the safety follow-up period will be presented based on the safety follow-up population.

Previous and concomitant medications are non-study medications. Concomitant therapy includes any medication used by a patient from the washout period until 28 days after the last dose of trial treatment. The previous and concomitant medication will be coded using the Genentech (GNE) drug dictionary. This is a proprietary Roche Dictionary which is used to code concomitant medications in the Trial Management System (TMS) coding tool. The Standardized Medication Name (CMDECOD), which is the medication generic

or combination generic as defined by the Drug Thesaurus (proprietary Genentech/Roche dictionary), and the Medication Class (CMCLAS), which is the primary medication class as defined by the Drug Thersaurus, will be used for the analyses.

Therapies will be classified as previous or concomitant as follows:

Previous: If the medication start date is prior to start of double-blind treatment,

Concomitant: If medication is taken at anytime between the start of double-blind treatment and 28 days after last positive dose of randomized treatment.

Post (safety follow-up): if the medication is taken during the safety follow-up period, i.e., on or after the first dose of open-label pirfenidone.

The number and frequency of previous and concomitant medications taken by patients in the two treatment arms will be presented by Medication Class and Standardized Medication Name. If patients receive more than one drug within a Medication Class or Standardized Medication Name they will be counted only once for the respective Medication Class or Standardized Medication Name.

A separated table will be presented for post medications during the safety follow-up period.

All medications will be listed identifying the previous/concomitant and post medications.

The missing imputation rules for the medication dates are described under section 4.8.

4.4.5 Compliance

With respect to the home-based daily measurements compliance of patients will be investigated. It will be analyzed if gaps of measurements occur over time. A gap is thereby defined as 7 or more than 7 consecutive days of missing measurements or non-accepted (borderline accepted or rejected) quality blows. A summary table displaying number of patients with gaps in daily measurements, number of gaps and duration of gaps will be provided by treatment arm for data from handheld spirometer.

4.5 EFFICACY ANALYSIS

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

The primary analysis of the primary efficacy endpoint of this study is planned to be performed when the last patient reached the date of the last follow-up visit after end of the double-blind treatment period (clinical cut-off date).

4.5.1 Primary Efficacy Endpoints

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 spirometer over the 24-week double-blind treatment period.

The primary null hypothesis (H0) is that the mean FVC decline for both treatments is equal:

$$H0: \mu 1 = \mu 2,$$

where μ1 denotes the mean FVC decline for patients receiving Pirfenidone, and μ2 denotes the mean FVC decline for patients receiving Placebo.

The primary alternative hypothesis (H1) is that the mean FVC decline for both treatments is not equal:

$$H1: \mu 1 \neq \mu 2$$

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 for the primary endpoint.

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 α=0.05.

The mean FVC decline for each treatment arm will be calculated using the estimated FVC decline for each individual patient. The estimated FVC decline for individual patients will be obtained by applying a linear regression model to all data points collected during the 24-week double-blind treatment period:

$$X_{it} = \alpha_i + \beta_i D_{it} + u_{it}$$

where

X_{it} = the FVC measurements (mL) of patient i on day t, with i=1,…,N and t=1,…,T, being N the total number of patients randomized and T the total number of days with assessment.

D_{it} = study day t of patient i

α_i, β_i = intercept and slope of the individual linear regression of patient i

The time-adjusted decline for patient i is then obtained by estimating the patients' individual difference in predicted values between baseline and week 24 from the linear regression.

In a further step, the time-adjusted mean FVC decline is estimated by calculating the mean over all individual time-adjusted declines of all patients by treatment arm.

A summary table displaying the mean FVC decline together with two-sided 95% confidence intervals based on percentiles of the t-distribution will be provided by treatment arm. The mean FVC decline in each treatment arm will be compared using a student's t-test with a two-sided significance level α=0.05

As a sensitivity analysis to the primary analysis, the time-adjusted mean FVC decline will be estimated by a repeated measures mixed model with patient effects fitted as random and day of measurement and treatment fitted as fixed effects. Please refer to Section 4.5.5 for further details.

A detailed description of SAS code to be used for the repeated measures mixed model is provided together with the respective table shell.

4.5.2 Secondary Efficacy Endpoints

For secondary endpoints, all data from baseline 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:

- Descriptive statistics for values and changes from baseline over time of all spirometry test parameters will be presented.

- 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

- The absolute change in percent predicted FVC measured by spirometry during site visits at week 24 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 concomitant MMF medication use (Yes/No), and the presence/absence of IPAF as defined by the MDT

- Absolute change from baseline to week 24 in percent predicted DLco will be compared between the treatment arms using a rank ANCOVA. Change from baseline to week 24 will be used as an outcome variable and standardized rank baseline value will be used as a covariate

- A summary table presenting the values of DLco (%) and its change from baseline will be presented over time and by treatment arm.

- The absolute 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
  - A summary table presenting the 6MWD parameters and their change from baseline will be presented over time and by treatment arm.
- The absolute change in UCSD-SOBQ total score will be analyzed using a rank ANCOVA model. The UCSD-SOBQ total 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 Please see section 4.5.4 for further details.
- The absolute change in Leicester Cough Questionnaire total score will be analyzed using a rank ANCOVA model. The Leicester Cough Questionnaire total score recorded at 24 weeks will be used as the outcome variable and standardized rank baseline Leicester Cough Questionnaire total score will be used as a covariate. Please see section 4.5.4 for further details.
- 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. Please see section 4.5.4 for further details.
- The change in total 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. Please see section 4.5.4 for further details.
- The time from randomization to the first occurrence of all-cause non-elective hospitalization and respiratory non-elective hospitalization will be analyzed using Kaplan-Meier (KM) techniques:
  - KM plots of time to first occurrence of the different events will be provided by treatment arm. Frequencies and percentages of patients with events and patients censored will be provided. Descriptive statistics of KM estimates of the time to first occurrence (weeks) will be presented.
  - Log-rank tests based on the time to the first event will be used to compare the two treatment arms.
  - Hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models in which the four groups from the two randomization stratification factors are included in the model.
- The incidence of investigator reported acute exacerbations in the two treatment arms will be compared with Fisher's exact test.
  - Incidence of, and time to first, investigator-reported acute exacerbations

- Progression free survival (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:
    - KM plots of time to first occurrence of the combined primary efficacy endpoint will be provided by treatment arm.
    - Frequencies and percentages of patients with events and patients censored will be provided. Descriptive statistics of KM estimates of PFS (weeks) will be presented.
    - The PFS of two randomized treatment arms will be compared with a log-rank test.
    - Hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models.
- An alternative definition of PFS (also in weeks), 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 as defined for the point above; 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 assessed by the SOC "Respiratory, thoracic and mediastinal disorders" (in weeks) will be analyzed using Kaplan-Meier techniques as defined above; 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.

4.5.3 Exploratory Efficacy Endpoints

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.

For the MMF objective, primary and selected secondary endpoints will be investigated by means of a subgroup analyses that stratifies patients according to whether they received MMF treatment. In addition, the overall safety summary will be presented by this subgroup. The selected secondary endpoints are:

- Deaths from any cause and respiratory disease-related
- Hospitalizations from any cause and respiratory disease-related

The analysis of these exploratory efficacy endpoints by subgroup are defined under section Section 4.5.6.

The mean FVC decline in each treatment arm will be calculated as in the primary analysis for the subgroups of patients that received MMF treatment and compared using a student's t-test with a two-sided significance level α=0.05. Exploratory efficacy endpoints are discussed in the sensitivity and subgroup sections (see Section 4.5.5 and Section 4.5.6, respectively).

Moreover, additional categorical analyses for the percent predicted DLco and 6MWD will be presented as exploratory:

- Categorical change of >15% absolute decline from baseline to week 24 in percent predicted DLco will be compared between the treatment arms using a logistic regression.
- Categorical change of >50% absolute decline from baseline to week 24 in 6MWD (m) will be compared between the treatment arms using a logistic regression.

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

4.5.4 Analyses of 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.

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. 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.

St. George´s Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantifies health-related health status in patients with chronic airflow limitations. The SGRQ is a 50-item questionnaire, addressing the frequency of respiratory symptoms (items 1 – 8), the patient's current state (sections 9 – 16). From the 50 items a total score, as well as three component scores (Symptoms, Activities, Impacts) will be derived. The total score ranges from 0, presenting the best possible health status to 100, presenting the worst possible health status.

The change in SGRQ total score will be of primary interest when assessing health-related quality of life (HRQoL).

The analysis of PROs assessed by SGRQ total score and by SGRQ component scores for symptoms, activity, and impacts will be analyzed as follows:

- The absolute score values and changes from baseline for the total and each sub-score will be presented descriptively over time by treatment arm.
- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate. This analysis will be done only for the total score.

The SGRQ and the details for calculating the score can be found in Appendix 3.

The University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)

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. Each of the 24 activities are rated on how dyspnea affects the activity on a 6-point scale: 0 = None at all to 5 = Maximal or unable to do because of breathlessness. The scores will be summarized to a total score, ranging from 0 – 120.

The total score of the UCSD SOBQ will be summarized as follows:

- The absolute total scores and changes from baseline will be presented descriptively over time by treatment arm.
- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

Additional details on the UCSD SOBQ can be found in Appendix 3

The Leicester Cough Questionnaire

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.

The total score and the physical, psychological and social domain scores of the Leicester Cough Questionnaire will be analyzed as follows:

- The scores and changes from baseline will be presented descriptively over time by treatment arm.

- Changes from baseline to week 24 or early discontinuation visit will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate. This analysis will be done only for the total score.

Details on calculating the domain scores can be found in Appendix 3

The Cough VAS

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

The cough VAS score will be summarized descriptively by visit and treatment arm. The change in cough VAS will be analyzed using a rank ANCOVA model. The change in VAS score for cough recorded at 24 weeks will be used as the outcome variable and the standardized rank baseline result will be used as a covariate. Please refer to Appendix 3 for further details.

4.5.5 Sensitivity Analyses

As a sensitivity analysis to the primary analysis, the time-adjusted mean FVC decline will be estimated by a repeated measures mixed model with patient effects fitted as random and day of measurement and treatment fitted as fixed effects. Corresponding model estimates will be tabulated.

A second model adding the stratification factors as covariates will be also presented.

Additional covariates such as gender, age and height that are used to determine FVC % predicted will be examined as well.

Additionally, the impact of different assumptions with respect to the variance-covariance matrix underlying the repeated measures mixed model will be investigated.

4.5.6 Subgroup Analyses

Subgroup analyses will be conducted for the exploratory endpoint, as described in Section 4.5.3. The following subgroups will be based on:

- The four groups resulting from combinations of the two stratification factors:
    - Concomitant MMF treatment (yes/no)
    - Presence/absence of IPAF as defined by the MDT
- Gender: Male, Female

- Age (years): <65 years, ≥ 65 years
- Percent predicted FVC at Baseline: <65%, ≥65% to < 80%, ≥80%
- Percent predicted DLco at Baseline: <35%, ≥35%
- Body weight: <60 kg, ≥60 kg

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

No pharmacokinetic or pharmacodynamic analyses are planned for this study.

4.7 SAFETY ANALYSES

All safety analyses of data from the double-blind treatment period will be based on the safety population, i.e., the safety population will include all randomized patients who received at least one dose of trial treatment, with patients grouped according to treatment received. Safety data from the follow-up period will be summarized based on the safety follow-up population.

The safety objective for this trial is to evaluate the safety of pirfenidone vs. placebo.

No formal statistical testing will be performed for safety parameters.

Data collected during the 12-month safety follow-up will be analyzed separately (see section 4.8).

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 4.03, 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) version 20.1 or higher 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 modifications and treatment interruptions. Adverse events leading to treatment interruption or dose modification will also be summarized.

Laboratory parameters including hematology and the chemistry panel will be presented in shift tables of NCI-CTCAE version 4.03 grade at baseline vs. worst grade during treatment period. The laboratory parameters will be presented according to means, standard deviation, minimum, and maximum. Selected laboratory parameters will be also graphically presented over time. Liver abnormalities for the parameters total bilirubin, alkaline phosphatase, ALAT (SGPT) and ASAT (SGOT)) will be also presented.

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

4.7.1 Exposure of Study Medication

All analyses described in this section refer to the data collected in the drug-log for the double-blind randomized treatment period. Unknown doses will be excluded from the exposure analyses.

4.7.1.1 Treatment duration

Summaries of dosing, treatment duration, dose interruptions or reductions during the randomized double-blind treatment period will be provided for each treatment arm separately.

The overall treatment duration (weeks), including and excluding dose interruptions, will be summarized descriptively by treatment arm. The overall treatment duration including dose interruptions will be defined as follows:

[Date of last positive dose of randomized treatment received (pirfenidone/placebo) – date of first intake of randomized treatment) + 1)] / 7.

The overall treatment duration excluding dose interruptions will be derived from the treatment administration panels using the time windows described above, considering only days on treatment. i.e. positive dose.

Details on treatment administration, reductions or interruptions will be listed.

4.7.1.2 Doses and Dose modifications or interruptions

The total dose (mg), the average daily dose (mg/d) and the last dose administered (mg/d) will be presented descriptively for each of the study treatments.

The average daily dose will be calculated by summing up the number of capsules taken, divided by the overall treatment duration including dose interruptions as defined above.

Numbers and proportions of patients with at least one dose modification, or drug interruption, will be presented for each treatment arm separately. Numbers and proportions of patients with 1, 2, 3 or more dose modifications, or treatment interruptions, will be given.

The total number of dose modifications, reductions or treatment interruptions, will be presented together with numbers and frequencies of reasons for dose modification, reduction or treatment interruption.

Dose modifications, reductions or treatment interruptions will be presented as given in the drug logs dose strength and number of capsules taken.

In addition, dose intensity will be analyzed descriptively by treatment arm over time. For calculation of dose intensities, the time from first administration of randomized treatment to the end date of randomized treatment will be considered. The following formula will be used for calculation:

Dose intensity (DI) = (total dose received / total dose planned)*100.

4.7.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to a preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Agencies (MedDRA®). MedDRA version 20.1 or above and related SMQ lists will be used for coding.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. For AEs of varying severity, the most severe grade as documented on the eCRF will be used in the summaries. An AE will be considered severe if the most extreme grade will be larger or equal to 3.

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. All adverse events will be reported until 28 days after the last dose of study drug. After this period, the Investigator should report any SAEs that are believed to be related to prior study drug treatment.

For safety analysis of the double-blind treatment period treatment-emergent adverse events (TEAEs) will be defined as:

- AEs that started or worsened on or after first intake of randomized treatment until last positive dose of randomized treatment + 28 days

Adverse events that are reported after informed consent but before the first intake of randomized treatment will be considered as non-treatment-emergent AEs. These might include AEs that occur during the screening period.

Post-treatment AEs are not expected to occur, but will be defined as AEs that are reported more than 28 days after the last dose of randomized treatment for patients who do not enter the 12-month safety follow-up period. Those AEs will be listed.

The analysis of AEs within the framework of the primary study analysis will focus on treatment-emergent AEs (TEAE).

An overview of patient safety profile will present the number and proportion of patients in each treatment arm experiencing:

- Any and any related treatment-emergent adverse events (TEAE)
- Any and any related serious treatment-emergent adverse events (serious TEAE)
- Any and any related severe treatment-emergent adverse events (TEAEs ≥ Grade 3)
- Any and any related TEAE of special interest (AESI). 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: [ALT or AST >3 x ULN + total bilirubin >2 x ULN]

- Any and any related hepatic side effects: elevations in ALT and AST >3 × ULN at the same timepoint in the study.
- Any and any related gastrointestinal (GI) disorder (MedDRA SOC: GI Disorders)
- Any and any related photosensitivity (MedDRA Preferred terms Photodermatosis, Photosensitivity reaction, Pruritus, Pruritus allergic, Pruritus generalized). Potential updates in those terms will be needed in case the MedDRA version changes.
- Any and any related rash (MedDRA Preferred terms Nodular rash, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash follicular, Exfoliative Rash, Solar dermatitis, Solar urticarial, Sunburn, Erythema, Dry skin). Potential updates in those terms will be needed in case the MedDRA version changes.
- Angioedema (MedDRA preferred term Angioedema).
- Dizziness (MedDRA preferred term Dizziness).
- Fatigue (MedDRA preferred term Fatigue).
- Weight loss (MedDRA preferred term Weight loss).
- Increase 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.
- Any and any related TEAE leading to death

- Any and any related TEAE leading to treatment discontinuation
- Any grade 3-4 laboratory liver test results
    - ASAT (SGOT) results
    - ALAT (SGPT) results
    - alkaline phosphatase results
    - total bilirubin results

The incidence of TEAEs, related TEAEs, non-serious TEAEs, serious TEAEs, related serious TEAEs, grade 3-5 TEAEs and TEAEs leading to treatment discontinuation, dose modification or death will be summarized by treatment arm, by system organ class (SOC) and preferred term (PT) on the basis of the safety population. Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Additionally the total numbers of TEAEs will be provided for each SOC and overall.

Similar summary presentations will be provided for the incidence of TEAEs leading to dose reduction and drug interruption and TEAEs leading to hospitalization.

Non serious Treatment-emergent Adverse Events with >5% frequency will be also presented by SOC and PT. In addition, Serious Treatment-emergent Adverse Events, Fatal serious TEAEs and serious TEAEs related to pirfenidone or placebo will be presented in the same table by SOC and PT.

A summary table presenting the numbers and frequency of patients with TEAEs by most extreme CTCAE Grade (Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5) will be provided for each SOC and PT by treatment arm. In case the most extreme intensity is missing, it will be replaced by the initial intensity. If both most extreme and initial intensity are missing, the AE will be included in the Grade ≥3 category and a category for “missing” will be added.

Further, Kaplan-Meier curves for time to onset of first adverse event of the most relevant related TEAEs will be provided by treatment arm when the number of events are enough to do the analyses. These will include the following PTs or groups of AEs: Nausea, Diarrhoea, Weight decreased, Fatigue, Decreased appetite, and photosensitivity, or rash. In addition, the analysis will be done for the SOC GI.

All adverse event data will be listed by patient number and study day of onset including a flag variable for identifying the period of the event (double-blind treatment period or safety follow-up period). If the AE does not belong to any of the perods, the period flag will be missing.

4.7.3 Deaths

Numbers and frequencies of deaths and of deaths occurring within 28 days after the last dose of double-blind treatment will be presented by treatment arm.

All information associated with deaths collected in eCRF panel on study discontinuation will be listed. A flag variable will be included in the listing specifying the study period when the death occurred.

4.7.4 Laboratory Data

All of the laboratory tests will be conducted by the trial site's local laboratory.

All parameters will be graded according to NCI CTCAE (CTEP 2010), version 4.03, if applicable. Laboratory parameters that cannot be graded according to the corresponding NCI CTCAE version 4.03 will be assessed with respect to normal range (low, normal, high).

Laboratory parameters including hematology and the chemistry panel will be presented in shift tables of NCI-CTCAE version 4.03 grade at baseline versus worst grade during randomized double-blind treatment period. The laboratory parameters will be presented according to means, standard deviation, minimum, and maximum. Selected laboratory parameters will be also graphically presented over time.

The following laboratory 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).

Clinical laboratory values will be presented separately for CTCAE-gradable and non-CTCAE gradable parameters by laboratory panel (hematology, serum chemistry). For laboratory analyses, visits will be assigned to visit windows as described in Section 4.9. This will also be valid for possible unscheduled visits. In case that multiple evaluable assessments occur within the same visit, the nearest to midpoints value will be used for analyses.

The following summaries will be prepared:

For each laboratory parameter, descriptive statistics of laboratory values at each scheduled visit (derived as described above), and absolute changes from baseline to post-baseline will be presented by treatment arm.

Shift tables presenting categorical changes in CTCAE grade from baseline to worst grade recorded during the double blind period, in the indicated direction, will be provided for CTCAE-gradable parameters by treatment arm. If no CTCAE grade is available for a specific laboratory variable, shift tables will present worst changes with respect to normal range category (low, normal, high).

Liver abnormalities (total bilirubin, alkaline phosphatase, ALAT (SGPT), ASAT (SGOT)) of Grade 3 and 4 will be presented showing numbers and percentages of patients for each parameter separately. Line graphs of liver parameters will be provided.

4.7.5 Vital Signs

Vital signs will include measurements of respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressures (mmHg) while the patient is in a seated position, temperature (C) and weight (kg). Vital signs will be assigned to visit windows as per Section 4.9. Descriptive statistics will be used to summarize vital signs data at baseline and at each scheduled post-baseline visit, and for the absolute change from baseline to each scheduled post-baseline visit by treatment arm during double-blind period.

4.7.6 ECG

Single ECG recordings will be obtained at specified time points, as outlined in the Schedule of Assessments (see Appendix 2), and may be obtained at unscheduled time points as indicated.

The following should be recorded in the appropriate eCRF: heart rate (beats/min), RR interval (msec), QRS interval (msec), PR duration (msec), uncorrected QT interval (msec), 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.

QTcF values of the safety population will be assigned to the following intervals: < 500 ms, 500–550 ms, and > 550 ms. Numbers and percentages of patients with their maximum QTcF interval category will be summarized by treatment arm over time. Absolute changes from the Baseline to each post-baseline visit in QTcF values will be categorized to < 31 ms, 31–60 ms, and > 60 ms. Numbers and percentages of patients in each category will be presented by treatment arm for each post-baseline visit or treatment discontinuation. Planned visits will be used for presentations.

Descriptive statistics for heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and the QTcF will be presented for each visit by treatment arm.

A listing containing ECG data will be presented.

4.8 SAFETY FOLLOW-UP ANALYSES

Data collected during the safety- follow-up period will be analyzed in the following way.

Adverse events during the 12-month safety follow-up period for pirfenidone treatment will be defined as:

- AEs that started or worsened on or after the date of safety follow-up period start until the end of the safety follow-up.

The safety follow-up population will be used for these analyses.

Summary tables for the incidence of AEs, related AEs, serious AEs, related serious AEs, severe AEs and severe related AEs will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages of patients experiencing (at least) one event in the respective category will be presented by decreasing frequencies. If patients have more than one AE within a SOC or PT they will be counted only once for the respective SOC or PT. Additionally, the total numbers of AEs will be provided for each SOC and overall. As with the end of the double-blind treatment period, an overview of safety will also be presented.

Pirfenidone exposure during safety-follow-up will be analyzed in a similar fashion as described in section 4.7.1 with regard to treatment duration and amount of drug intake.

Data of laboratory assessments (AST, ALT, bilirubin, and alkaline phosphatase) and vital signs during safety-follow-up period will be analyzed in a similar fashion as described in section 4.7.4 and 4.7.5.

Data will be presented by randomized treatment labeled as ‘Randomized Pirfenidone’ and ‘Randomized Placebo’.

4.9 MISSING DATA

In general, missing data will not be imputed. Exceptions will be made for the data related to adverse events and concomitant medications as described below.

For adverse events, missing start dates will only be imputed for determination of whether the adverse event is considered to be treatment-emergent or not.

Incomplete or missing onset dates will be imputed to the earliest date possible (using any reliable portions of the onset date that are available). The onset day is considered unreliable if the month or year portions of the date are missing.

In case the month portion of the AE start date is missing, the AE start date will be imputed to the earliest day possible by using the following principles:

- If Treatment Start Date is missing, then the AE Start Date will be imputed as 01-01-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

- When the Treatment Start Date is not missing, and the years of AE Start Date and Treatment Start Date coincide, the AE onset date will be set to the Treatment Start Date

- When the Treatment Start Date is not missing, and the years of the AE Start Date and the Treatment Start Date do not coincide, then the AE Start Date will be imputed as 01-01-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

In case the day portion of the AE Start Date is missing, the AE Start Date will be imputed to the earliest day possible as follows:

- If the Treatment Start Date is missing, then the AE Start Date will be imputed as 01-MMM-YYYY or the earliest date regarding signature of informed consent, screening date or randomization date, whichever is the later one

- When the treatment date is not missing, and the years and months from the AE Start Date and the Treatment Start Date coincide, the AE onset date will be set to the Treatment Start Date

- When the Treatment Start Date is not missing, and AE Start Date is after the Treatment Start Date according to the given year or month, then the AE Start Date will be imputed as 01-MMM-YYYY

If the AE stop date is missing, then the event will be assumed to be ongoing and a stop date will not be imputed.

In the case the treatment end date is missing and it cannot be judged whether the event occurred during the period of Treatment Start Date to Treatment End Date plus 28 days, the AE will be considered treatment-emergent as long as it is not flagged as prior AE.

For imputation and handling of missing intensity or relationship to study medication, please see Section 4.7.2.

All other missing or incomplete adverse event data will be left as missing.

For concomitant medications, missing start or end dates will only be imputed to determine whether the medication is considered to be prior, on-treatment, post-treatment.

In general if only the day is missing from the start date then the missing day will be imputed as 01-MMM-YYYY unless the month is the same month as the start of study medication in which case the missing date will be imputed as the treatment start date.

If both the day and month are missing from the start date then the start date will be imputed as 01-JAN-YYYY.

If both the day and month are missing from the start date year is the same as treatment start date then the start date will be imputed as 'treatment start date', but if the year is after treatment start date, the start date will be imputed as 01-JAN-YYYY.

If the day, month and year are all missing from the start date then the start date will be imputed as 01-JAN for the year in which the patient was recruited to the study.

If the day, month and year are all missing from the start date then the start date will be imputed as 'treatment start date'.

If an incomplete stop date has both the year and month present, the day will be imputed as the last day of the month or date of discontinuation/death.

If the AE is ongoing at time of primary analysis, concomitant medication will be summarized for the double-blind treatment period and safety follow-up.

4.10 VISIT WINDOWS

Visit windows for double-blind treatment period will be applied to vital signs and laboratory data and the derived visits will be used in the by-visit summarizations. If multiple observations fall within the same visit window, the observation with the nearest to midpoint value will be used in the analysis, if not stated otherwise. If subjects discontinue from the double-blind treatment period early the data will be assigned to the early discontinuation visit. The date of early discontinuation will be considered as the target date.

The "Baseline" visit is a derived data point to identify baseline values which are used to calculate the change from baseline values. Baseline is defined in section 4.2.2

The End of Treatment [EOT] visit will either be a copy of early discontinuation records for patients who prematurely discontinued double-blind treatment period or Week 24 records for patients who completed the double-blind treatment period.

Table 2 Visit Windows

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	1	Last valid assessment prior to first intake of randomized study drug (pirfenidone/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (pirfenidone/placebo) was given.
Week 4 [4]	28	One day after first dose of randomized treatment to 42
Week 8 [8]	56	43 to 70
Week 12 [12]	84	71 to 98
Week 16 [16]	112	99 to 126
Week 20 [20]	140	127 to 154

Week 24 [24]	168	155 to a maximum of 195 if the patient did not early discontinued.
Early discontinuation [25]	Not applicable	As occurred
End of treatment (EOT) [26]	Not applicable	As occurred
Follow-up visit (FUP1) [27]	Not applicable	As occurred
Safety follow-up visits(SFUP) [28]	Not applicable	As occurred: Month 1 to 6: Monthly visits Month 7 to12: Approximately every 3 months
Additional Safety follow-up visit [29]	Not applicable	As occurred: up to 12 months plus 28 days

4.11 INTERIM ANALYSES

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.

No formal interim analyses for efficacy are planned.

4.12 BIOMARKER ANALYSES

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 2).

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.

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

Analyses on biomarker data will not be in the scope of this SAP, but will be planned and described separately.

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Appendix 1
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 Appendix 3
Patient Reported Outcome Questionnaire

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 of the CSP) 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. 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. 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. A Follow-up Visit will occur 28 days after the end of the 24-week double-blind treatment period.

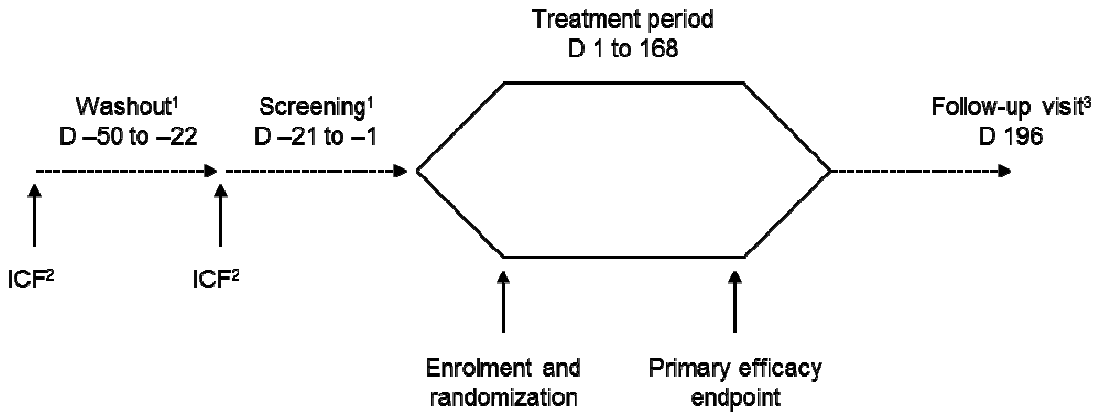
After completion of the double-blind treatment period and the Follow-up Visit at Week 28, the Sponsor will offer the possibility to the patients to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the safety follow up period, the patients 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 Appendix 3
Patient Reported Outcome Questionnaire
below.

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 2). 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.

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.

Appendix 2
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											

	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	
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			
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	

	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	
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			

	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	
UCSD-SOBQ [q]			x			x			x	x			
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			

	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	
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.

[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. 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.

a.

Appendix 3
Patient Reported Outcome Questionnaire

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	None of the time

					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.						

Scoring

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.

The scores from each of the following questions are added together to provide the mean score for each domain:

1. Physical: 1, 2, 3, 9, 10, 11, 14, 15
2. Psychological: 4, 5, 6, 12, 13, 16, 17
3. Social: 7, 8, 18, 19

Domain scores: total score from items in domain/number of items in domain (range 1–7).

Total scores: addition of domain scores (range 3–21).

UCSD-SOBQ

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

Scoring

Twenty one items assess the severity of shortness of breath during specific activities associated with daily living if patients do not routinely perform the activity, they are asked to estimate the degree of shortness of breath anticipated. Three additional items ask about limitations due to: shortness of breath, fear of harm from overexertion and fear of shortness of breath.

Each of the 24 activities are rated on how dyspnea affects the activity on a 6-point scale:

0 = None at all to 5 = Maximal or unable to do because of breathlessness

The scores from all 24 questions are totalled to provide a score in the range 0 – 120.

SGRQ

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
☐	☐	☐	☐	☐

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continued...

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 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 ☐

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 these days.

	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	☐	☐

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	☐	☐

USA / US English version 4

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

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

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems:***

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

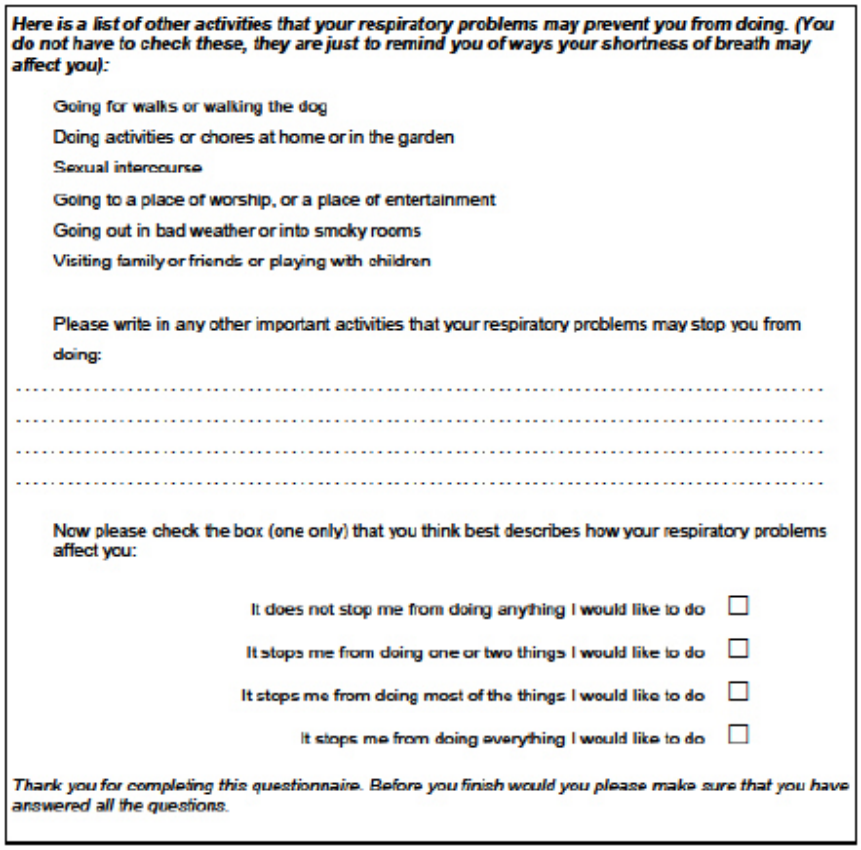
Section 7

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

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems:***

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

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.

STRUCTURE OF SGRQ

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in patients with diseases of airways obstruction.

Part 1 (Questions 1-8) addresses the frequency of respiratory symptoms. It is not designed to be a precise epidemiological tool, but to assess the patient's perception of their recent respiratory problems.

Part 2 (Sections 9-16) addresses the patient's current state (i.e. how they are these days).

The Activity score measures disturbances to daily physical activity. The Impacts score covers a range of disturbances of psycho-social function. Validation studies for the original SGRQ showed that this component relates in part to respiratory symptoms, but it also correlates quite

strongly with exercise performance (6-minute walk test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

Three component scores are calculated for the SGRQ

Symptoms – concerned with the effect of respiratory symptoms their frequency and severity

Activity concerned with activities that cause or are limited by breathlessness

Impacts covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease.

Total score summaries the impact of disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

SGRQ SCORES IN HEALTHY SUBJECTS

Means (95% confidence intervals) for SGRQ scores in normal subjects with no history of respiratory disease

N	Age-years	FEV1 as % predicted	Symptoms score	Activity score	Impacts Score	Total Score
72	46 (17 - 80)	95 (91-99)	12 (9-15)	9 (7-12)	2 (1-3)	6 (5-7)

Scoring

Questions 1 – 7 The eCRF screens should be set up so that where a patient has ticked a box, a value of 1 is entered for the appropriate question. By default, the empty boxes are entered as 0. Where a patient has missed a question the cells on the spreadsheet are left blank. Example: Response = 1c, 'Over the last year I have coughed a few days a month'. A value of 1 is entered for 1c and a value of 0 is entered for 1a, 1b, 1d and 1e. If no tick was present for question 1 then 1a to 1e would be left blank.

Question 8 Where a patient has ticked 'Yes' to having a worse wheeze in the morning, a value of 1 is entered for the appropriate question. All other responses are entered as 0. Example: Do you have a wheeze? = 'Yes' and Worse in the morning = 'Yes'. then response to question 8 = 1. Do you have a wheeze? = 'Yes' and Worse in the morning = 'No'. Or, Do you have a wheeze? = 'No'. then response to question 8=0.

Questions 9, 10 & 17 Where a patient has ticked a box, a value of 1 is entered for the appropriate question. The empty boxes are entered as 0. Where a patient has missed the question the cells on the spreadsheet are left blank. Example: Response = 10a, 'My chest trouble made me stop work'. A value of 1 is entered for 10a and a value of 0 is entered for 10b and 10c. If no tick was present for question 10, then 10a to 10c would be left blank.

Questions 11 – 16 Where a patient has ticked 'True' a value of 1 is entered for the appropriate question and where a patient has ticked 'False' a value of 0 is entered. Where a patient has missed a question the cell on the spreadsheet is left blank.

Example: 15a = 'True' then 15a = 1.

14c = 'False' then 14c = 0.

13h = missing then 13h is left blank

In response to question 14, if a patient is not receiving medication, enter the responses as zero, otherwise the calculator will read the values as missing.

Missing Questions

There should not be any missing items in the questionnaire, but the SGRQ can have up to 24% of missing items in the questionnaire. If more than 24% of items are missing the scores will be missing.

ITEM WEIGHTS

Once the questions have been answered the following weights are applied to the individual responses

PART 1

Over the past 3 months, I have coughed:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
80.6	63.2	29.3	28.1	0.0

Over the past 3 months, I have brought up phlegm (sputum):

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
76.8	60.0	34.0	30.2	0.0

3) Over the past 3 months, I have had shortness of breath:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
87.2	71.4	43.7	35.7	0.0

4) Over the past 3 months, I have had attacks of wheezing:

Most days/week	Several days/ week	A few days a month	Only with chest infections	Not at all
86.2	71.40	45.6	36.4	0.0

5) During the past 3 months, how many severe or very bad unpleasant attacks of chest trouble have you had?

More than three	3 attacks	2 attacks	1 attack	None
86.7	73.5	60.3	44.2	0.0

6) How long did the worst attack of chest trouble last?

a week or more	3 or more days	1 or 2 days	Less than a day	None
89.7	73.5	58.8	41.9	0.0

7) Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

No good days	1 or 2 good days	3 or 4 good days	Nearly every day	Every day
93.3	76.6	61.5	15.4	0.0

8) If you have a wheeze, is it worse in the morning?

No	Yes
0.0	62.0

PART 2

The weights in Part 2 are also applied to the individual responses to each question. The worse the impact the higher the weight. This means that weights are not applied sequentially in the order that the response is given.

9) How would you describe your chest condition?

The most important problem I have	83 .2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0

10) If you have ever had paid employment?

My chest trouble made me stop work	88.9

My chest trouble interferes with my work or made me change my work	77.6
My chest trouble does not affect my work	0.0

11) Questions about what activities usually make you feel breathless.

Sitting or lying still	90.6
Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or games	72.1

12) More questions about your cough and breathlessness.

My cough hurts	81.1
My cough makes me tired	79.1
I get breathless when I talk	84.5
I get breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84.0

13) Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I do not expect my chest to get any better	82.3
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5

14) Questions about your medication.

My medication does not help me very much	88.2

I get embarrassed using my medication in public	53.9
I have unpleasant side effects from my medication	81.1
My medication interferes with my life a lot	70.3

15) Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81.0
I walk more slowly than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle,swim fast or play competitive sports	63.5

16) We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do housework	79.1
I cannot move far from my bed or chair	94.0

17) Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do	0.0
It stops me doing one or two things I would like to do	42.0
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

SCORING ALGORITHM

Three component scores are calculated: **Symptoms; Activity; Impacts**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive response are summed.

ii The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.

iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

Score = 100 x Summed weights from positive items in that component

Sum of weights for all items in that component

The Total score is calculated in similar way:

Score = 100 x Summed weights from positive items in the questionnaire

Sum of weights for all items in the questionnaire

Sum of maximum possible weights for each component and Total:

Symptoms 662.5

Activity 1209.1

Impacts 2117.8

Total 3989.4

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient).

It will be noted that the questionnaire requests a single response to questions 1-7, 9-10 and 17. If multiple responses are given to one of these questions then averaging the weights for the positive responses for that question are acceptable

SYMPTOMS COMPONENT

This is calculated from the summed weights for the positive responses to questions 1-8.

ACTIVITY COMPONENT

This is calculated from the summed weights for the positive responses to questions 11 and 15.

IMPACTS COMPONENT

This is calculated from the summed weights for the positive responses to questions 9-10, 12- 14 and 16-17.

TOTAL SCORE

The Total score is calculated by summing all positive responses in the questionnaire and

expressing the result as a percentage of the total weight for the questionnaire

HANDLING MISSED ITEMS

There should not be any missed items but if there are missing items the scores should be calculated using the following rules:

following should be used: The following method is recommended for missing items:

Symptoms

The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4).

Activity

The Activity component will tolerate a maximum of 4 missed items. The weight for the

missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4).

Impacts

The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4).

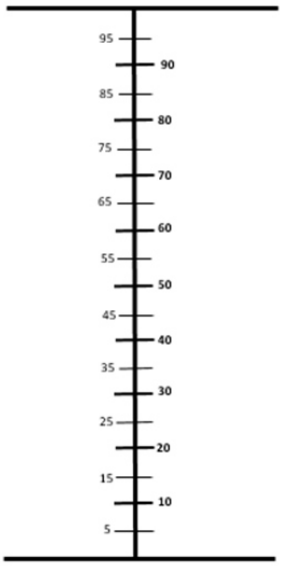
This visual analogue scale is designed to help us learn about the severity of your cough. This scale is 100mm (10cm) in length.

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.

Cough Visual Analogue Scale (VAS)

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