STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SILDENAFIL ADDED TO PIRFENIDONE IN PATIENTS WITH ADVANCED IDIOPATHIC PULMONARY FIBROSIS AND RISK OF GROUP 3 PULMONARY HYPERTENSION**

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STUDY DRUG:	**Pirfenidone (Esbriet®) and Sildenafil (RO0280296)**
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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Not applicable, as this is the first version of the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALAT	Latin American Thoracic Society
ALT	Aalanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AV	Atrioventricular
BCE	Biostatistical Computing Environment
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
Cmax	Maximum concentration
COPD	cChronic obstructive pulmonary disease
CRP	C-reactive protein
CSP	Clinical study protocol
CYP	Cytochrome
DBP	Diastolic blood pressure
DLco	Carbon monoxide diffusing capacity/ pulmonary diffusing capacity
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEMEA	Eastern Europe, Middle East, and Africa
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
ERK1/2	Extracellular regulated kinases 1 and 2
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAP	Gender, age and physiology
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GI	Gastrointestinal
GNE	Genentech drug dictionary
GWAS	Genome-wide association study
HLT	High level term
HR	Hazard ratio
HRCT	High-resolution computed tomography

HRQoL	Health related quality of life
5-HT	Serotonin
ICF	Inform Consent Form
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IL	Interleukin
ILD	Interstitial lung diseases
IMP	Investigational medicinal product
IND	Investigational New Drug
IPF	Idiopathic pulmonary fibrosis
IRB	Independent review board
ITT	Intent-to-treat
IxRS	Interactive voice or web-based response system
JRS	Japanese Respiratory Society
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure
6MWD	6-minute walk distance
6MWT	6-minute walk test
NAC	N-acetylcysteine
NAION	Nonarteritic ischemic optic neuropathy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
O2	Oxygen
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PDE5	Phosphodiesterase-5
PDGF	Platelet-derived growth factor
PDMS	Protocol Deviation Management System
PFS	Progression-free survival
PFTs	Pulmonary function tests
PH	Pulmonary hypertension
PK	Pharmacokinetics
PRO	Patient reported outcome
PP	Per-protocol
PT	Preferred Term
QD	Daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cells
RHC	Right heart catheterization
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

SGRQ	Saint George's Respiratory Questionnaire
SMQ	Standardized MedDRA queries
SOC	System Organ Class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SPF	Sun protection factor
SpO2	Oxyhemoglobin saturation
TAPSE	Tricuspid annular plane systolic excursion
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TID	Three times daily
TRV	Tricuspid regurgitation velocity
UCSD SOGQ	University of California San Diego Shortness of Breath Questionnaire
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UV-A	Ultraviolet A
UV-B	Ultraviolet B
WBC	White blood cells
WHO	World Health Organization

1. BACKGROUND

As described in the Clinical Study Protocol (CSP, Section 1.3), the diagnosis of idiopathic pulmonary fibrosis (IPF) carries a bleak prognosis, with progressive disability due to respiratory insufficiency (Hallstrand et al. 2005). Pulmonary hypertension (PH) is a major contributor to morbidity and mortality in patients with advanced IPF with an adverse impact on survival (Nadrous et al. 2005, Lettieri et al. 2006.). This study is designed to assess the treatment of patients with advanced IPF who have evidence suggesting PH, which is most likely caused by IPF.

While drugs used to treat PH have either not been effective for treatment of IPF (bosentan, ambrisentan, macicentan) or are unlikely to be able to address the parenchymal changes in the fibrotic process, anti-fibrotic drugs are unlikely to have any notable effect on the perfusion aspects of interstitial lung diseases (ILDs). Therefore, combination treatment appears as a promising approach to the major clinical problem of combined IPF and PH (Wuyts et al. 2014).

In this study, pirfenidone (Esbriet®) administration will be combined with sildenafil (generic formulation). As sildenafil induces vasodilatation preferentially in well-ventilated lung areas, such vasodilatation could improve ventilation-perfusion matching and thus gas exchange in patients with IPF (Ghofrani et al. 2002). The combination of pirfenidone and sildenafil represents a promising approach to treat patients with advanced IPF and secondary PH.

The expected benefits of the sildenafil/pirfenidone combination relate to the anticipated improvements in both pulmonary hemodynamics and pulmonary function. A reduction in pulmonary vascular resistance by sildenafil would be expected to improve mean pulmonary artery pressure (mPAP), reducing strain on the right ventricle and improving cardiac output, assuming that left ventricular function and systemic vascular resistance are not adversely affected. Secondary benefits, such as reduced risk of right heart failure, cardiac arrhythmias, cardiac-related hospitalizations, and cardiac-related death might also ensue. Improvement in ventilation/perfusion matching by sildenafil would be expected to improve gas transfer in the lung. An increase in oxyhemoglobin saturation, along with an improvement in cardiac output, would be expected to have a beneficial effect on functional exercise capacity. These possible benefits of sildenafil, together with the known benefits of pirfenidone in slowing the rate of decline in lung function, might have a benefit on reducing respiratory decompensation and related hospitalizations.

The Sponsor is expecting that the benefit-risk comparison for patients participating in this study of pirfenidone with sildenafil is positive.

2. STUDY DESIGN

This is a Phase IIb, randomized, placebo-controlled, multicenter, international study of the efficacy, safety, and tolerability of combination treatment with sildenafil and pirfenidone in patients with advanced IPF and risk of Group 3 PH, who have been on pirfenidone treatment in a dose range of 1602 to 2403 mg/day for at least 12 weeks with demonstrated tolerability.

Approximately 176 patients will be enrolled at approximately 75 clinical centers in Canada, Europe (EU) and Eastern Europe, Middle East, Africa (EEMEA), and potentially Asia-Pacific. Patients who are withdrawn from the study will not be replaced.

On providing written informed consent, patients will be instructed to stop taking their commercial pirfenidone and start taking the study-provided pirfenidone.

Patients will also be required to discontinue all prohibited medications and undergo a 28-day Washout Period. After completing the Washout Period, patients will enter a Screening Period, which lasts up to 28 days; during Screening, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. Patients that are not taking a prohibited medication will forgo the Washout Period and enter Screening directly.

A run-in period will be provided for countries where patients will not be able to take pirfenidone for 12 weeks due to reimbursement issues. After signing the informed consent form, the 12 week run-in pirfenidone supply will be provided by the Sponsor.

In summary, the study consists of 5 phases:

- Run-in period of 12 weeks (if needed)
- Screening period
    - +/- 28-day washout period (if needed); this can be part of the run-in period if the run-in period is applicable.
    - Screening period (up to 28 days). Patients will be evaluated for eligibility based on the inclusion and exclusion criteria
- Double-blind treatment period (52 weeks)
- Follow-up period (4 weeks)
- Additionally, there will be the possibility for patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56, for up to 11-months safety follow-up. During this time the patients should be evaluated by the treating physician approximately every three months.

2.1 PROTOCOL SYNOPSIS

Please refer to the Protocol Version 2, 01 December 2017 (and its Appendices).

2.2 OUTCOME MEASURES

The primary objective for this study is to investigate the efficacy, safety and tolerability of sildenafil compared with placebo when added to pirfenidone in patients with advanced IPF and risk of Group 3 PH.

2.2.1 Primary Efficacy Outcome Measures

The primary objective of the study is to evaluate the efficacy of adding sildenafil compared with placebo, to pirfenidone treatment.

The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

Relevant decline in 6-minute walk distance (m) (6MWD) of at least 15% from baseline (as defined below*), respiratory-related non-elective hospitalization, or all-cause mortality

* Relevant decline in 6MWD from baseline is defined as:

- Any decline >25% from baseline or
- A decline between 15-25% from baseline, if accompanied by at least one of the following:
    - worsening of SpO2 desaturation (%) at the end of the 6-minute walk test (6MWT) compared to baseline
    - worsening of the maximum Borg scale at the end of the 6MWT compared to baseline
    - increased O2 (L) requirements at the end of the 6MWT compared to baseline.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment.

The secondary efficacy endpoints are the followings:

- Progression-free survival (PFS), defined as time to decline in 6MWD of ≥15% compared with baseline as defined in Section 2.2.1, respiratory-related non-elective hospitalization, or death from any cause
- Proportion of patients with decline in 6MWD of ≥15% from baseline as defined in Section 2.2.1

- Time to respiratory-related non-elective hospitalization
- Time to death from any cause
- Lung transplantation
- Time to all-cause non-elective hospitalization
- Time to respiratory-related death
- Change from baseline in transthoracic echocardiography (ECHO) parameters
- Change from baseline in pulmonary function tests (PFTs)
- Change from baseline in SpO2 at rest and during the 6MWT (end of test and lowest SpO2)
- World Health Organization (WHO) Functional Class
- Dyspnea (assessed by the University of California San Diego Shortness of Breath Questionnaire [UCSD SOGQ])
- Health-related quality of life (HRQoL) (assessed by the Saint George's Respiratory Questionnaire [SGRQ])
- Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) level

2.2.3 Patient-Reported Outcome Measures

Patient-reported outcomes (PROs) will be used to assess health-related quality of life (HRQoL) and Dyspnea. The two questionnaires used are:

- HRQoL assessed by the SGRQ
- Dyspnea assessed by the UCSD SOBQ

2.2.4 Safety Outcome Measures

The safety objective for this study is to evaluate the safety of adding sildenafil compared with placebo to pirfenidone treatment on the basis of the following endpoints:

- Nature, frequency, severity, relationship and timing of treatment-emergent adverse events (TEAEs)
- Changes in vital signs
- Clinical laboratory test results
- 12-lead electrocardiograms (ECGs)
- Exposure to study drug

- Study discontinuation or study drug discontinuation

2.3 DETERMINATION OF SAMPLE SIZE

There are no reference data available on the use of pirfenidone in this patient population with a measurable DLco ≤ 40% of predicated value and mPAP ≥ 20 mmHg on right heart catheterization (RHC). A total sample size of approximately 176 patients is planned, and patients will be randomized 1:1 to the two treatment groups. The statistical hypothesis for the treatment comparison is based on the proportion of patients who experienced a ≥15% decline from baseline in 6MWD, were hospitalized for cardiac- or respiratory non-elective reasons, or who died, according to a pooled analysis of the effects observed in the pirfenidone groups of three large Phase III trials (CAPACITY 1, CAPACITY 2, and ASCEND).

The planned sample size is based on the primary endpoint, proportion of patients with disease progression, and assumes 80% power and a one-sided significance level of 5%. Given the disease progression rate of 72% by 52 weeks in the three large registration trials for pirfenidone, and assuming an additive effect of sildenafil on pirfenidone, a disease progression rate of 54% in the combination treatment group is assumed and an absolute difference of 18% (respectively a relative reduction of 25%) in disease progression rates is considered a clinically meaningful treatment benefit.

Patients who are withdrawn from the study will not be replaced.

2.4 ANALYSIS TIMING

Independent data monitoring committees will meet approximately every three months to review the accumulating safety data. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

The primary analysis of the primary endpoint will be performed when all data points are collected on the database up to the last patients last visit (LPLV) that is planned to occur at week 56 after randomization of the last patient into the study. Therefore, the primary analysis of the study will be conducted when all patients completed the 52 weeks treatment phase and the mandatory 4 weeks follow-up visit.

An analysis of the safety follow-up data will be performed approximately one year after the primary analysis for this study has been conducted.

3. STUDY CONDUCT

The study design is described in Section 2. After the double-blind treatment period (52 weeks or early discontinuation + 4 weeks follow-up) the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol or up to 11-months safety follow-up.

Following, there will be two parts for the analysis:

- Analysis of efficacy and safety data recorded during the double-blind treatment period
- Summary of safety data recorded during the 11-month follow-up period when patients receive pirfenidone alone.

3.1 RANDOMISATION, BLINDING AND UNBLINDING PROCEDURES

Patients will be randomized 1:1 to receive either pirfenidone plus sildenafil or pirfenidone plus placebo. The randomization process will be conducted using a validated interactive voice or web-based response system (IxRS). To guard against systematic selection bias and ensure comparability of treatment groups, the randomization will be stratified by availability of a previous RHC (yes/no) and by FEV1/FVC ratio below/above 0.8 to ensure an equal distribution of patients with some degree of pulmonary obstruction in both treatment groups.

To maintain the double-blind nature of the study, the sildenafil and placebo treatments will be identical in appearance (see Protocol Section 4.3.1.2).

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

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct approximately every three months. Efficacy data will only be provided if requested by the iDMC. For details please see Section 4.11.

4. STATISTICAL METHODS

Generally, presentations will be provided for each treatment group.

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 group 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).

If not otherwise specified, changes will denote absolute changes and will generally be changes from baseline to the corresponding time point.

Where data will be summarized over time, the following time points will be presented, as applicable: baseline, weeks 1, 3, 6, 12, 19, 26, 32, 39, 45, 52, follow-up visit and early discontinuation visit.

Safety data recorded in the 11-month follow-up period will be presented in a separate summary as described in Section 4.8.

Where applicable other analysis methods will be specified below.

4.1 ANALYSIS POPULATIONS

4.1.1 All patients enrolled

All patients enrolled are all patients that signed the Inform Consent Form (ICF).

4.1.2 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 groups 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 randomized treatment completion date or the date of early discontinuation, collected on the early discontinuation eCRF page for patients not completing the planned 52 weeks of treatment.

4.1.3 Per Protocol Population

Not applicable.

4.1.4 Safety Population

The safety population will include all randomized patients who have received at least one nonzero or positive dose of randomized study drug (sildenafil/placebo). Patients in the safety population will be assigned to treatment groups according to the treatment they received (actual treatment).

All safety analyses for the double-blind period will be performed from the first day of randomized sildenafil/placebo treatment until treatment completion/discontinuation date plus 28 days.

4.1.5 Safety Follow-up Population

The safety follow-up population will be defined as all patients who have received at least one positive dose of pirfenidone after the end of double-blind treatment period without being completed or discontinued from the study.

Safety analyses for the 11-month follow-up period will be performed during the safety follow-up period, which starts 29 days after end of double-blind period until end of study.

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.

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 up to the date of the first intake of randomized study drug (sildenafil/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. Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given. Adverse events occurring on the date of first randomized sildenafil/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)

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)

On-treatment assessments will be the assessments performed on or after the date of first dose of randomized sildenafil/placebo treatment until the double-blind treatment completion or discontinuation date plus 28 days.

4.2.5 Assessments during 11-months Safety Follow-up Period

Details of adverse events recorded during the 11-month safety follow-up period will be presented. This period starts 29 days after the date of completion of double-blind treatment period for patients who completed the double-blind period and received a positive dose of Pirfenidone after end of double-blind period, without being completed or discontinued the study. The safety follow-up period ends with the study completion/discontinuation visit, with a maximum of 11 months. 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 primary analysis at the end of the double-blind treatment period is defined as the date when the last patient completes the last visit of the double-blind treatment period (LPLV) or the date at which the last data point which is required for the statistical analysis (primary analysis) is received, whichever is the later date. LPLV for the primary analysis is expected to occur approximately 56 weeks after the last randomized patient begins the double-blind treatment period.

There will be a second cut-off for the end of the study when all patients have completed the 11-months safety follow-up which is expected to occur approximately 52 weeks after the LPLV for the primary analysis.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

To ensure the comparability of the treatment groups, the randomization will be stratified by the availability of a previous RHC (yes/no) and by FEV1/FVC ratio (<0.8, ≥0.8) to ensure an equal distribution of patients with pulmonary hypertension assessed based on RHC (‘gold standard’) or echo and an equal distribution of patients with some degree of pulmonary obstruction in both treatment groups respectively.

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.

The number and percentage of patients that fall into each of the four groups based on the two stratification factors will be presented by treatment group, including the frequencies of patients for each category as per eCRF.

The differences between the stratification factors provided by IxRS and the data collected in the eCRF will be listed. Outputs for concordance between the stratification factors by eCRF and by IxRS will also be presented.

4.4 ANALYSIS OF STUDY CONDUCT

All analyses described in this section will be performed on the ITT population, presenting data by treatment group: pirfenidone/sildenafil and pirfenidone/placebo.

4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients (enrolled), participating in run-in, failed run-in, screened, failed screening, randomized, treated, completed or early discontinued the double-blind treatment period, patients entering the 11-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.

The following definitions will be used:

- Patients enrolled: All patients who have signed informed consent,
- Participating in run-in: All patients that participated in the 12-week prior run-in period. These are the patients that signed the inform consent, received at least one dose of pirfenidone in the corresponding drug-log and had a screening date later with about 3 months compared to the ICF signature.
- Run-in failures: All patients that participated in the prior run-in period but were not eligible for the study. These are the patients that participated in the run-in period but answered “No” to question in the eCRF Subject Eligibility page: “Did Patient meet all eligibility criteria?” and they did not fill screening visit.
- Patients screened: All patients who have a screening visit,
- Patients screened having run-in period: All patients who have a screening visit and participated in the run-in period.
- Patients screened without run-in period: All patients who have a screening visit and did not participate in the run-in period.
- Screening failures: All the patients screened who have filled “Did Patient meet all eligibility criteria?” = “No”
- Patients randomized: All patients who have been randomized to receive either sildenafil or placebo, i.e. have a randomization date.

- Patients randomized and not treated, if any: 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.

- 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 from the study: patients who answered “Yes” to the question “Did the Patient early discontinued from the study?” on the Study Completion/Early Discontinuation eCRF form and they gave a primary reason of discontinuation.

    - Early discontinuation from study within 28 days after double-blind treatment end, for patients who didn’t enter the safety follow-up period.

    - Early discontinuation from study entering the 11-month safety follow-up period.

- Patients who completed the study: patients who answered “Yes” to the question “Did the Patient complete the study?” on the Study Completion/Early Discontinuation eCRF form.

- Patients ongoing, if any: patients who didn’t fill the Study Completion/Early Discontinuation eCRF form.

An overview on patient’s enrolment by country and center will be provided. In addition, a frequency table of enrollment by country and center will be also presented.

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

A listing including disposition information and the screening/run-in failure reasons will be also created.

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 PDMS, reviewed by the medical monitors, and will be provided in a SAS dataset via Valicert. 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, tobacco and substance use history will be summarized by descriptive statistics or frequency tables.

Demographics

The following demographic characteristics will be summarized by treatment group:

- Age (years): as entered in the eCRF at the screening visit.
- Age categories: 18 – 64 years, 65 - 84 years, ≥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.
- NT-proBNP (pg/mL) at baseline.

Demographic data will be also listed.

Data on female reproductive status will be presented descriptively; methods of contraception will only be listed within the demographic listing.

Tobacco Use History and Substance Use

The history of tobacco use will be summarized 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.

Numbers and percentages of patients for following characteristics by treatment group will be presented to specify substance use:

- Current substance use (yes/no).

- Substance use (cannabinoids, amphetamines, opiates, benzodiazepines, barbiturates, cocaine, nicotine, other).

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 21.1 or above and will be summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT) by treatment group. 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 will be also presented.

WHO Functional Class and GAP Score and Index at Baseline

The number and percentage of patients with baseline WHO functional class and GAP assessments recorded; and the number of patients that fall into each category will be summarized by randomized treatment group.

RHC and ECHO Tests at Screening and Baseline

RHC is used to identify patients with risk of Group 3 PH. In absence of a previous RHC, a peak tricuspid regurgitation velocity (TRV) ≥ 2.9 m/s from ECHO assessment will be used for identification of patients with risk of Group 3 PH.

- Right heart catheterization (RHC) *(Screening)*:
    - Is RHC available? (yes/no)
    - Mean pulmonary artery pressure (mPAP) (mmHg),
    - Pulmonary artery wedge pressure (PAWP) (mmHg).
- Transthoracic echocardiography (ECHO) parameters (Screening):
    - Was ECHO performed during Screening? (yes/no),
    - Peak tricuspid regurgitation velocity ≥ 2.9 m/s (yes/no)

The number and percentage of patients with previous RHC available at Screening will be summarized. The mPAP and PAWP will be summarized using descriptive statistics by randomized treatment group. The numbers and percentages of patients with ECHO performed during Screening and the numbers and percentages of patients with Peak tricuspid regurgitation velocity (TRV) > 2.9 m/s will be presented.

- Transthoracic echocardiography (ECHO) parameters (Baseline):
    - Peak tricuspid regurgitation velocity (TRV) (m/s),
    - PAPs (mmHg),

The number and percentage of patients with ECHO performed at baseline will be presented and the baseline TRV (m/s), PAPs (mmHg), Tricuspid annular plane systolic excursion (TAPSE) (cm), Right ventricle basal diameter (cm), Inferior vena cava diameter (cm) and Left ventricular ejection fraction (LVEF) (%) values will be summarized using descriptive statistics by randomized treatment group.

Time from IPF Diagnosis

The time in years since the original IPF diagnosis will be calculated as:

((Date of randomization – Date of IPF diagnosis) + 1) / 365.25,

and will be summarized descriptively by randomized treatment group. The number and percentage of patients with a history of emphysema and historical high-resolution computed tomography will also be presented. Descriptive statistics of the time from most recent historical high-resolution computed tomography (years) will be presented. As above, the date of randomization will be used as reference date for calculation of duration.

Historical Pulmonary Function Test (PFT)

The number and percentage of patients who performed pulmonary function 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.

- Carbon monoxide diffusing capacity (DLco) (mmol/min/kPa and % predicted)
- DLco/Va (KCO) (mL/min/mmHg/L and %)
- Forced vital capacity (FVC) (L and % predicted)
- Forced expiratory volume in 1 second (FEV1) (L and % predicted)
- FEV1 (L) / FVC (L) ratio (1)

These historical pulmonary function test parameters will be summarized using descriptive statistics by treatment group. Both, absolute and percent predicted values will be presented. A listing of historical pulmonary function test will be also presented.

Pulmonary Function Test (PFT) at Baseline

The values recorded for the baseline assessments of the pulmonary function tests

- Carbon monoxide diffusing capacity (DLco) (mmol/min/kPa and % predicted)
- DLco/Va (KCO) (mL/min/mmHg/L and %)
- Forced vital capacity (FVC) (L and % predicted)
- Forced expiratory volume in 1 second (FEV1) (L and % predicted)

- FEV1 (L) / FVC (L) ratio (1)

will be summarized using descriptive statistics by treatment group.

Historical surgery or procedure assessments

A listing of historical surgeries or procedure assessments will be presented.

6 Minute Walking Test (6MWT) at Baseline

The 6MWD measures the distance a patient is able to walk quickly on a flat, hard surface in a period of 6 minutes. The 6MWT will be performed according to standard procedures (ATS Statement, 2002) described in the Procedure Manual.

At Day 1, 6MWT will be performed twice and the better of the two 6MWT values will be reported as the baseline value. For each 6MWT, information on SpO2, Borg scale and O_2 requirements will be collected.

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 Oxygen (O2) (yes/no)

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

The values of the parameters recorded for the 6-minute walking distance test

- 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 and lowest SPO2 during the test),
- Borg scale result (at the end of the test),
- Oxygen (O2) requirements (L) (at the end of the test)

will be summarized descriptively by treatment group.

Stratification Factors

The number and percentage of patients that fall into each of the four groups based on the two stratification factors:

- previous RHC available (yes, no),
- FEV1/FVC ratio (<0.8, ≥0.8)

will be presented by treatment group. The stratification factors will be listed. In addition, a table of concordance between stratifications and a frequency table presenting the factors as per IxRS and as per eCRF will be created.

Previous Pirfenidone Treatment

The number and percentage of patients that started with previous pirfenidone treatment during a run-in period and patients that were pretreated with commercial pirfenidone prior to entering the study will be presented. The duration of previous pirfenidone treatment (weeks) before screening during run-in, as commercial pirfenidone and both will be summarized descriptively, and it is defined as: ((screening date – first previous pirfenidone treatment taken) + 1) / 7.

4.4.4 Previous and Concomitant Medication

Previous and concomitant medications are non-study medications. The previous and concomitant medication will be coded using the WHOdrug dictionary.

Therapies will be classified as previous or concomitant as follows:

Previous: If the medication end date is prior to randomization date,

Concomitant: If medication is taken anytime between the randomization date and 28 days after the double-blind treatment completion/discontinuation.

All medications will be listed.

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

4.5 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be based on data recorded by patients in the ITT population with patients grouped according to planned randomized treatment.

4.5.1 Primary Efficacy Endpoints

The primary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment in patients with advanced IPF and risk of group 3 PH.

The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

Relevant decline in 6MWD of at least 15% during the double-blind treatment period (≥15% from baseline (as defined below*), respiratory-related non-elective hospitalization, or all-cause mortality, during the double-blind treatment period).

*Relevant decline in 6MWD from baseline is defined as:

- Any relative decline >25% from baseline or
- A relative decline between 15-25% from baseline, if accompanied by at least one of the following:
    - worsening of SpO2 desaturation at the end of the 6MWT compared to baseline: a worsening of SpO2 desaturation at the end of the 6MWT compared to baseline will be defined as any decrease in SpO2 (%) during double-blind treatment period.
    - worsening (increase) of the maximum Borg scale at the end of the 6MWT compared to baseline during double-blind treatment period.
    - increased O2 requirements at the end of the 6MWT compared to baseline: an increase in O2 requirements will be defined as any increase of at least 1 liter during the double-blind treatment period.

A flow chart demonstrating how the different criteria will be used to identify the combined endpoint can be found in Appendix 2.

As patients will not have to discontinue the treatment once they have experienced the combined endpoint, it may happen that a patient will experience the combined endpoint more than once, but only the first occurrence will be taken into account for the analysis of the primary endpoint.

Patients who discontinue treatment prematurely will be analyzed based on the available data at the time of discontinuation or data from the last available visit. No imputation method will be applied. Patients who undergo lung transplantation during the study will be withdrawn from the study at the time of hospitalization for transplantation.

A Chi-square test with a one-sided significance level $\alpha = 0.05$ will be used to compare disease progression rates between the two randomized treatment arms. The risk difference of disease progression rates (Sildenafil vs. Placebo) together with the corresponding Clopper-Pearson 95% confidence interval will be presented.

Sensitivity analyses will be performed as described in Section 4.5.5 below.

4.5.2 Secondary Efficacy Endpoints

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

- Progression-free survival (PFS) defined as the time to first occurrence of the combined primary efficacy endpoint (decline in 6MWD of ≥15% compared with baseline, respiratory-related non-elective hospitalization, or death from any cause) as per Section 4.5.1 will be analyzed using Kaplan-Meier (KM) techniques.
    - KM plots of time to first occurrence of the combined primary efficacy endpoint will be provided by treatment group.
    - Frequencies and percentages of patients with events and patients censored will be provided. Descriptive statistics of KM estimates of PFS will be presented, together with KM estimates and 95% confidence intervals for 1, 3, 6, 12, 19, 26, 32, 39, 45 and 52 weeks survival event free rates.
    - The PFS of two randomized treatment groups will be compared with a log-rank test.
    - Hazard ratios and corresponding 95% CI will be calculated by applying an unstratified Cox-proportional hazard models.

  Patients that do not experience the combined endpoint as defined above during the double-blind treatment period will be censored at the time of double-blind treatment completion/discontinuation.

The single components of the combined primary efficacy endpoint (as defined in Section 4.5.1) will be further analyzed as follows:

- The relevant decline in 6MWD will be assessed as
    - Proportion of patients with at least one decline in 6MWD of ≥15% from baseline (as defined in Section 4.5.1). Number and percentage of patients with a relevant decline will be presented by treatment arm and a Chi-square test with a one-sided significance level α=0.05 will be applied to compare the two treatment groups.

- Descriptive statistics for 6MWD will be provided for each visit, together with the changes from baseline to each visit.

  - The number and percentage of patients that performed the 6MWT, rested for at least 10 minutes, stopped the test before 6 minutes and required O2 will be summarized by randomized treatment group and by visit.

  - The values and change from baseline of the parameters recorded (distance walked (m), oxygen requirements (L), Borg scale result, and values recorded pre-, during and post-test for SPO2 (%), heart rate (beats/min), systolic blood pressure (mmHg) and diastolic pressure (mmHg)) will be summarized descriptively by treatment group and by visit. Additionally, a shift table will be presented summarizing categorically the distance walked (<300m, ≥300m) by treatment group and visit.

- The change in 6MWD (m) from baseline to 12 months will be analyzed using a rank ANCOVA model with the change from baseline as the outcome variable and standardized rank baseline 6MWD as a covariate. Patients who discontinue treatment prematurely will be analyzed based on the available data at the time of discontinuation or their last available visit. No imputation method will be applied.

- All-cause and respiratory related non-elective hospitalization: a frequency table will be provided displaying number of patients with at least one non-elective hospitalization and the number of non-elective hospitalizations. The duration of the hospitalization (weeks) will be also presented descriptively. A frequency table presenting the number of patients with acute exacerbations (triggered or idiopathic) and the number of acute exacerbations will be also presented. Acute exacerbations will be defined as presented by Collard et al, 2016. Please refer to Appendix 8 for further specifications.

- The time from randomization to first occurrence (or admission) of each of the following events will be analyzed using Kaplan-Meier techniques:

  - Respiratory-related non-elective hospitalization, all-cause non-elective hospitalization, all-cause mortality, respiratory-related death and acute exacerbation. For acute exacerbations, the admission date of the related hospitalization will be used as occurrence date.

  - 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 will be presented, together with KM estimates and 95% confidence intervals for 1, 3, 6, 12, 19, 26, 32, 39, 45 and 52 weeks survival event free rates.

- Log-rank tests based on the time to the first event (e.g. first hospitalization respiratory-related non-elective hospitalization) 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.

Patients that do not experience the parameter of interest by the time of completion/ discontinuation from the double-blind treatment period will be censored. The end date of the double-blind treatment period will be used as censoring date, if none of the specific censoring rules, as presented below, will apply.

The following specific censoring rules will be applied:

- Respiratory-related non-elective hospitalization (collected in the respiratory-related hospitalizations eCRF page): If the patient is hospitalized as a result of a respiratory-related condition before the end of the double-blind treatment period, the time from randomization to the first event will be calculated. Patients that do not experience the event will be censored at the date of double-blind treatment period completion/discontinuation. This will also apply for patients that are hospitalized for any other reason.

- All-cause mortality: If the patient dies for any reason before the end of the double-blind treatment period, the time from randomization to the death will be calculated. Patients that are alive at their completion/discontinuation of the double-blind treatment period will be censored at that time point.

- All-cause non-elective hospitalization (taken from AE eCRF page): If the patient is hospitalized for any reason before the end of the double-blind treatment period, the time from randomization to the first event will be calculated. Patients that do not experience the event will be censored at the date of completion/discontinuation of the double-blind treatment period.

        - Respiratory-related mortality: if the dies as a result of a respiratory related condition before the end of the double-blind treatment period, the time from randomization to the death will be calculated. Patients that are alive at their completion/discontinuation of the double-blind treatment period will be censored at that time point. Patients that die as a result of other causes during the double-blind treatment period will be censored at their date of death.

- Absolute values and change from baseline to end of treatment for the following ECHO parameters will be summarized by visit and treatment group:
    - Peak tricuspid regurgitation velocity (m/s)
    - PAPs (mmHg)
    - TAPSE (tricuspid annular plane systolic excursion) (cm)
    - Right ventricle basal diameter (cm)
    - Inferior vena cava diameter (cm)
    - LVEF (Left Ventricular Ejection Fraction) Result (%)
- Pulmonary function tests (PFTs), i.e. FVC (L and % predicted), FEV1(L and % predicted), FEV1 (L) /FVC (L) ratio (1), and carbon monoxide diffusing capacity (DLco) (mmol/min/kPA and % predicted) and DLco/Va (KCO) (mL/min/mmHg/L and % predicted) will be summarized by treatment group and analyzed in terms of
    - absolute values recorded and absolute changes from baseline by visit in actual and % of predicted values will be summarized descriptively for all parameters described above,
    - 5% and 10% categorical changes of FVC (%) from baseline will be summarized including the following categories: decline ≥10%, death or lung transplantation; decline of <10% but ≥5%; decline of <5% but ≥0%; improvement of >0% but <5%; and improvement of ≥5%. A Cochran-Mantel-Haenszel test will be applied to the categorical change comparing sildenafil and placebo.
    - The change from baseline to week 52 of FVC (%) 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.

- A summary table presenting the linear slope analysis using a mixed model for the FVC (L) decline from baseline to week 52 will be also presented.

- The number and percentage of patients that have lung transplantation will be presented by treatment group. Information on the number of patients with lung transplantation will be taken from the study discontinuation eCRF page.

- The number and percentages of patients in each of the four categories of WHO Functional Class will be presented over time by treatment group.

- GAP stages and index scores taken from the eCRF will be summarized categorically and descriptively over time by treatment group. Please refer to Appendix 4 for further details.

- Absolute values and changes from baseline in NT-proBNP levels will be summarized descriptively over time by treatment group.

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

Exploratory efficacy endpoints are discussed in the subgroup sensitivity analysis and biomarker sections.

4.5.4 Analyses of Patient-Reported Outcomes

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify the 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.

For details on calculation of SGRQ scores please see Appendix 6 and Appendix 7.

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

HRQoL assessed by SGRQ total score and by SGRQ component scores for symptoms, activity, impacts and total score will be analyzed as follows:

- The absolute score values and changes from baseline for each SGRQ score will be presented descriptively over time by treatment group.

- For the total score only, changes from baseline to week 52 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.

- Line graphs for the total score will be presented.

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 items will be rated on a 6-point scale. The scores will be summarized to a total score, ranging from 0 – 120, from best to worse health status.

Additional details on the UCSD SOBQ can be found in Appendix 5.

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

- The absolute total score and changes from baseline will be presented descriptively over time by treatment group.

- Changes from baseline to week 52 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.

- Line graphs for the total score will be presented.

4.5.5 Sensitivity Analyses

A sensitivity analysis of the proportion of patients with a decline of at least 15% in the 6MWD in the ITT population will compare disease progression rates in each treatment arm using a logistic regression model.

In addition, the Cochrane-Mantel-Haenszel test described above will be presented stratified by the stratifications factors (the availability of RHC and FEV1/FVC ratio) with a one-sided significance level $\alpha = 0.05$, as per eCRF and IxRS separately.

Moreover, the primary endpoint analysis will be repeated during the following time period in order to assess the impact of events shortly after end of treatment: from randomization to 28 days after completion/discontinuation of the randomized treatment.

Additional analysis of the change in 6MWD from baseline to 52 weeks will follow the approach taken in the Step-IPF publication (2010) using a linear mixed model with slope measurements for fixed effects estimated from baseline to Week 52 to compare the two treatment groups. Only patients with at least three measurements will be included in the analysis. The model will also include additional baseline covariates of age, sex, race,

height at baseline and Dlco (%) at baseline. The estimated treatment effect and 95% confidence intervals will be provided. The same model will be developed for the change in FVC (L) from baseline to 52 weeks.

Further sensitivity analyses will follow the approach taken with the Step-IPF publication (2013) in which a multivariable linear regression estimated the change in 6MWD as a function of treatment group, cardiac parameters from ECHO (Peak tricuspid regurgitation velocity, PAPs, TAPSE [tricuspid annular plane systolic excursion], Right ventricle basal diameter, Inferior vena cava diameter and LVE [Left Ventricular Ejection Fraction]), and interactions between treatment group and the cardiac parameters.

The time to multiple events (e.g. hospitalization before death) will be analyzed using the Anderson-Gill counting process approach to Cox models, where outcome (event [hospitalization, decline of at least 15% in 6MWD, death], no event) at the end of each interval is analyzed. This approach means that all events experienced by the patients can be included in the analysis and not just specific events or the time to first event.

Covariates can also be added to the model, they can either be baseline values or the value recorded at the start of the interval. The two randomization stratification factors will also be included in the model.

The frequency and percentage of patients with and without corridor card ID change among the study will be presented by treatment arm, presenting frequencies for 0, 1, 2, etc number of changes in the corridor card ID.

In order to measure the change from baseline in NT-proBNP during the double-blind treatment period among the different treatment arms, a mixed model with repeated measures per planned visit will be developed including the treatment and the baseline NT-proBNP value as covariates.

4.5.6 Subgroup Analyses

Subgroup analyses will be conducted for primary and selected secondary endpoints, as: decline in 6MWD of ≥ 15% from baseline, FVC categorical decline, PFS of the combined efficacy endpoint, hospitalizations and ECHO parameters summary. When possible, a forest plot presenting the results of all subgroups will be developed.

The following subgroups will be defined:

- RHC as collected in the eCRF: Yes, No,
- FEV1/FVC ratio as collected in the eCRF: <0.8, ≥0.80,
- Gender: Male , Female,

- Age (years): <65, ≥65,
- PAPs (mmHg) from ECHO assessment at randomization: <40 mmHg , ≥40 mmHg,
- Percent predicted FVC at baseline: <50%, ≥50%,
- Percent predicted DLco at baseline: ≤25% ,>25%,
- GAP index at baseline: GAP I, GAP II, GAP III,
- Body weight: <60 kg, ≥60 kg,
- BMI: <25 kg/m*2, ≥25 kg/m*2 to ≤30 kg/m*2 and >30 kg/m*2,
- With/without corridor card ID change,
- 6MWD at baseline: <300 m, ≥300 m,
- History of Emphysema from Pulmonary Function Test History: Yes, No,
- Patients that died/not died,
- NT-proBNP normal/abnormal: <1 x ULN, ≥1 x ULN.

The number of patients in each subgroup will be tabulated.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

No pharmacokinetic or pharmacodynamic analyses are planned for this study.

4.7 SAFETY ANALYSES

The safety objective for this study is to evaluate the safety of adding sildenafil compared with placebo to pirfenidone treatment on the basis of the following analyses.

The safety population will be used to present the safety analyses which will include all randomized patients who received at least one dose of randomized study drug (sildenafil or placebo), with patients grouped according to treatment received.

No formal statistical testing will be performed for safety parameters.

Data collected during the 11-month safety follow-up (i.e. adverse event and deaths) will be analyzed separately.

4.7.1 Exposure to Study Medication

Patients participating in this study are to be on a stable dose of pirfenidone for 28 days prior to Screening. At the Screening visit patients will be instructed to stop taking their commercial pirfenidone and start taking the study-provided pirfenidone. Patients that will not be able to take pirfenidone for 12 weeks prior to Screening due to reimbursement issues will be supplied with study pirfenidone during a 12-week run-in period.

Therefore, patients participating in the 12-week run-in period will enter all information on pirfenidone intake prior to screening into the drug log. A summary table with the duration of the previous pirfenidone treatment during run-in period will be presented as stated in section 4.4.3 . Patients not requiring run-in will enter information on pirfenidone intake into the drug log from the screening visit onwards. Information on previous commercial pirfenidone will be reported as concomitant medication.

Previous pirfenidone intake during run-in period will be listed together with randomized treatment period drug log information.

It is expected that pirfenidone will be administered during the whole double-blind treatment period, with exception of days of treatment interrupted. Randomized treatment (sildenafil/placebo) will be added to pirfenidone at or after randomization.

The main focus will be on the double-blind treatment period. Sildenafil/placebo treatment will be considered from the date of first randomized sildenafil/placebo treatment up to the date of last positive dose of randomized sildenafil/placebo treatment. Pirfenidone treatment will be considered from the date of first randomized sildenafil/placebo treatment up to date double-blind treatment was completed, or date of early treatment discontinuation. This information will be selected from the eCRF page “Double blind treatment completion/Early discontinuation”.

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

4.7.1.1 Treatment duration

The overall treatment duration (weeks) during the double-blind treatment period, including and excluding dose interruptions, will be summarized descriptively. The overall treatment duration including dose interruptions (weeks) will be defined as follows:

Pirfenidone:

- Overall pirfenidone treatment duration including dose interruptions (weeks) = [(Date of double-blind treatment completion (completers) or date of early treatment discontinuation (for patients who early discontinued treatment) as per eCRF – date of first intake of randomized pirfenidone treatment during double-blind treatment period + 1)] / 7.

Sildenafil/placebo:

- Overall sildenafil/placebo treatment duration including dose interruptions (weeks) = [(Date of last positive dose of randomized (sildenafil/placebo) treatment – date of first intake of randomized (sildenafil/placebo) 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 and interruptions will be listed.

4.7.1.2 Doses and Dose modifications or interruptions

The total dose (g), the last daily dose administered (mg) and the average daily dose (mg/d) for each of the study treatments will be presented descriptively. 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 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, or treatment interruptions, will be presented together with numbers and frequencies of reasons for dose modification, or treatment interruption.

Dose modifications or treatment interruptions will be presented as given in the drug logs.

4.7.2 Discontinuations from double-blind treatment period

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

4.7.3 Discontinuations from the study

KM plots for time to study discontinuation will be provided for all randomized patients and by randomized treatment, from the randomization date to the date subject discontinued from the study, as per eCRF. If the patient completed the study, the patient will be censored to the date of study completion.

4.7.4 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 21.1 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.

4.7.4.1 Adverse events prior to the double-blind treatment period

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, or during the pirfenidone run-in period, if applicable.

The numbers and percentages of patients with any AEs and any AEs related to pirfenidone will be summarized by randomized/not randomized patients, SOC and PT based on the number of patients enrolled. Related AEs are AEs that were considered to be related to Pirfenidone during the run-in period only. If the relationship of the adverse event is missing, it will be considered as related to Pirfenidone.

4.7.4.2 Adverse events during double-blind treatment period

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

For safety analyses on the double-blind treatment period treatment-emergent adverse events will be defined as:

- AEs that started or worsened on or after first intake of randomized treatment (sildenafil/placebo) until completion/discontinuation of double-blind treatment period + 28 days.

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

- Any and any related treatment-emergent adverse events (TEAEs)
- Any and any related serious treatment-emergent adverse events (serious TEAEs)
- Any and any related severe treatment-emergent adverse events (TEAEs ≥ Grade 3)

- Any and any related TEAEs of special interest (AESI) as recorded in the eCRF and defined as an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law; and suspected transmission of an infectious agent by the study drug.

- Any and any related gastrointestinal (GI) disorders (MedDRA SOC: GI Disorders)

- Any hepatic side effects (MedDRA AEGT: Esbriet - Potential Hy's Law AEGT' see Appendix 3)

- Any and any related clinically significant vascular event, defined as any TEAE included in at least one of the following AE groups:

    - Any and any related ischemic heart disease (MedDRA SMQ: Ischemic heart disease)

    - Any and any related cerebrovascular event (MedDRA SMQ: Central nervous system vascular disorders)

    - Any and any related bleeding event (MedDRA SMQ: Haemorrhages)

    - Any and any related thromboembolic event or pulmonary oedema (SMQ Embolic and thrombotic events and MedDRA Preferred term PT: pulmonary oedema)

    - Any and any related hypotension event (MedDRA high level term (HLT): Vascular hypotensive disorders)

- Any and any related photosensitivity or rash (MedDRA Preferred terms Nodular rash, Photodermatosis, Photosensitivity reaction, Pruritus, Pruritus generalised, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Solar dermatitis, Solar urticaria, Sunburn, Erythema, Dry skin)

- Any and any related visual effects (MedDRA Preferred term (PT): Optic ischaemic neuropathy)

- Any and any related priapism (MedDRA Preferred terms (PT): erection increased, priapism, painful erection)

- Any and any related TEAEs leading to death

- Any and any related TEAEs leading to treatment discontinuation

- Any grade 3-4 laboratory liver test results

- Any grade 3-4 AST (SGOT) results
- Any grade 3-4 ALT (SGPT) results
- Any grade 3-4 Alkaline phosphatase results
- Any grade 3-4 Total bilirubin results

Related TEAEs summarized in the safety profile will be considered to be either related to pirfenidone or related to sildenafil/placebo, or to both treatments.

If relationship to study drug is missing, the event will be considered to be related to both pirfenidone and sildenafil/placebo.

The incidence of TEAEs, related TEAEs, serious TEAEs, related serious TEAEs, severe TEAEs and related severe TEAEs will be summarized by treatment group, 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 of pirfenidone/sildenafil gorup. 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. Summary tables associated with TEAEs that are considered to be related to study drug will be presented as follows: TEAEs related to pirfenidone or sildenafil/placebo, TEAEs related to pirfenidone and sildenafil/placebo, TEAEs related to pirfenidone, TEAEs related to sildenafil/placebo.

Similar summary presentations will be provided for the incidence of TEAEs leading to hospitalization, TEAEs leading to treatment discontinuation (from pirfenidone, silfenafil/placebo or both), and TEAEs leading to death.

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 sildenafil/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 group. 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 TEAEs will be provided by treatment group. These will include the following PTs or

groups of AEs: Hypotension, Weight decreased, Fatigue, visual effects, or priapism. One Kaplan-Meier curve per PT and treatment group will be created.

4.7.4.3 Adverse events after the double-blind treatment period

Post-treatment AEs will be defined as AEs that are reported more than 28 days after the end date of double-blind treatment period. If a patient has a post-treatment AE but do not enter the safety follow-up period, then those AEs will be listed. If a patient has a post-treatment AE during safety follow-up period, please refer to section 4.8 for further details on the analysis of these AEs.

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.

4.7.5 Deaths

Numbers and frequencies of all cause deaths, as well as of respiratory-related deaths and deaths due to other cause will be presented by treatment group.

Numbers and frequencies of deaths occurring within 28 days after end date of double-blind treatment period, and within/after the first 168 days will be presented in the same way.

All information associated with deaths collected on 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.

Deaths during safety follow-up period will be summarized separately.

4.7.6 Pregnancies

Pregnancy test results will be listed together with demographics, presenting the date and study day of pregnancy test and test result.

4.7.7 Laboratory Data

The majority of laboratory parameters will be assessed by a central laboratory although local laboratories will be used to assess parameters in some countries. Unplanned local laboratory data might be available for patients that have central laboratory support but will not be used for the analyses. In addition, local laboratory parameters not collected at central laboratory will not be presented in the analyses. All values provided by local laboratories will be standardized and converted to SI units by DM. The reference ranges from the local laboratories will be applied, if available. Otherwise, global standard ranges will be used.

The results of urine pregnancy tests will be determined locally and will be recorded in the eCRF.

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).

For laboratory parameters and specific age ranges, the upper limit of normal provided by the central laboratory might be higher than the criterion for Grade 1 in NCI CTCAE. In such cases, the definitions provided in the NCI CTCAE, corresponding version 4.03 will be followed. This means that a shift of a laboratory value above the ULN that corresponds to a grade 2 abnormality or higher will be reported as such. Grade 1 abnormalities will not be reported for such situations.

Laboratory values that are reported to be below the limit of quantification (e.g. '<2') will be considered as to be 'LOW' for presentation in shift tables, if the value (e.g. '2') equals the lower limit of normal. The value as such (e.g. '2') will be used for descriptive statistics.

The following laboratory parameters will be collected:

- Hematology: complete blood count with platelet count and automated differential, i.e. hemoglobin, hematocrit, red blood cells [RBC], platelet count, white blood cells [WBC] with differential [including neutrophils, lymphocytes, monocytes, eosinophils and basophils

- Serum chemistry: glucose, blood urea nitrogen [BUN], creatinine, sodium, potassium, bicarbonate, total protein, albumin, total bilirubin, direct and total bilirubin, alkaline phosphatase, aldosterone, lactate dehydrogenase [LDH], AST, ALT, gamma-glutamyl-transferase [GGT]), C-reactive protein [CRP] and NT-proBNP, aldosterone

- Serum pregnancy test, urine dipstick for pregnancy testing (local).

For creatinine and pregnancy test result no grading as per NCI CTCAE, version 4.03 is possible.

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 value nearest to the midpoint will be used for analyses. Unscheduled local laboratory values that were collected for patients with central laboratory support will not be considered for selection, and will therefore not be presented in shift tables or summary statistics.

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 group.

Shift tables presenting categorical changes in CTCAE grade from baseline to worst grade recorded during the double blind period for safety analyses, in the indicated direction, will be provided for CTCAE-gradable parameters by treatment group. 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).

For CTCAE-gradable parameters, numbers and percentages of patients with laboratory values of grade 3 and 4 will be presented over time by treatment group.

Liver abnormalities (total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT)) of grade 3 and 4 will be presented showing numbers and percentages of patients for each parameter separately, as well as in combination with at least one of the parameters elevated post-baseline by treatment group. Line graphs of liver parameters and NT-proBNP will be provided.

Laboratory data for the parameters BNP, CPR and liver toxicities will be listed with values for both SI units and original, if available, being presented.

4.7.8 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure), respiratory rate, body weight and body temperature assessments 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 group. Line graphs for systolic and diastolic blood pressure will be provided. The body mass index (BMI) will only be provided at baseline and presented with the demographic data.

4.7.9 ECG

ECG assessments will be assigned to visit windows as per Section 4.10.

QTcF values will be assigned to the following intervals: < 500 ms, 500–550 ms, and > 550 ms. Numbers and proportions of patients with their maximum QTcF interval category will be summarized by treatment group at Screening, Baseline (Week 1), Week 26 and Week 52 or early discontinuation. Absolute changes from the Baseline to each post-baseline visit in QTcF values will be categorized to ≤ 30 ms, 31–60 ms, and > 60 ms. Numbers and proportions of patients in each category will be presented by treatment group for each post-baseline visit.

Descriptive statistics for heart rate and QTcF and changes from baseline for each visit will be presented by treatment group.

4.8 SAFETY FOLLOW-UP ANALYSES

Data collected during the safety- follow-up period will be analyzed based on the safety follow-up population.

Treatment-emergent adverse events during the 11-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 study.

The overview safety table presented for the double-blind treatment period will be repeated for safety follow-up period.

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.

All AEs collected during safety follow-up period will be listed together with the ones at double-blind treatment period.

Deaths during the safety follow-up period will be tabulated as described in section 4.7.5 and listed together with deaths during the double-blind treatment period.

Data will be presented by planned randomized treatment labeled as ‘Randomized pirfenidone + sildenafil’ and ‘Randomized pirfenidone + 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.

For imputation and handling of missing intensity or relationship to study medication, please see Section 4.7.4.

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.

For previous pirfenidone treatment, recorded in the concomitant medication eCRF that started before informed consent, missing month and day for the start year will be imputed with July 1st of the respective year. If the day is unknown, the 15th of the respective month will be imputed. Imputations will only be used for calculation of duration of previous pirfenidone 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 year is the same as treatment start date then the start date will be imputed as 'treatment start date', but if the 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 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 event 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

To ensure that recorded data are summarized at appropriate intervals, visit windows will be applied 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 value nearest to midpoint will be used in the analysis. If subjects discontinue from the study early the data will be assigned to the early discontinuation visit.

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.

Table 2 Visit Windows for 6MWT, laboratory data, vital signs, WHO functional class (Assessments made at every planned visit)

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)

Baseline [0]	*1*	Last valid assessment prior to first intake of randomized study drug (sildenafil/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given.
Week 3 [3]	22	One day after first dose of randomized treatment to 33 (17 to 27)
Week 6 [6]	45	34 to 67 (40 to 50)
Week 12 [12]	90	68 to 112 (85 to 90)
Week 19 [19]	135	113 to 157 (130 to 140)
Week 26 [26]	180	158 to 202 (175 to 185)
Week 32 [32]	225	203 to 247 (220 to 230)
Week 39 [39]	270	248 to 292 (265 to 275)
Week 45 [45]	315	293 to 340 (310 to 329)
Week 52 [52]	365	341 to maximum of 392
Early discontinuation from double-blind period [53]	Not applicable	As occurred
Follow-up visit	393	Vital signs only: as occurred

Table 3 Visit Windows for ECG, ECHO and weight data

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	*1*	Last valid assessment prior to first intake of randomized study drug (sildenafil/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given.
Week 26 [26]	180	One day after first dose of randomized treatment to 272 (175 to 185)
Week 52 [52]	365	273 to maximum of 392

Early discontinuation [53]	Not applicable	As occurred
Follow-up visit	393	Weight only: as occurred

Table 4 Visit Windows for Borg scale, DLCo, spriometry tests and GAP score

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	*1*	Last valid assessment prior to first intake of randomized study drug (sildenafil/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given.
Week 12 [12]	90	One day after first dose of randomized treatment to 135 (85 to 90)
Week 26 [26]	180	136 to 225 (175 to 185)
Week 39 [39]	270	226 to 315 (265 to 275)
Week 52 [52]	365	316 to maximum of 392
Early discontinuation [53]	Not applicable	As occurred

Table 5 Visit Windows for NT-ProBNP, CRP, aldosterone and urinalysis

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	*1*	Last valid assessment prior to first intake of randomized study drug (sildenafil/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given.
Week 1 [1]	1	First dose of randomized treatment.
Week 12 [12]	90	One day after first dose of randomized treatment to 135 (85 to 90)
Week 26 [26]	180	136 to 272 (175 to 185)

Week 52 [52]	365	273 to maximum of 392
Early discontinuation [53]	Not applicable	As occurred

Table 6 Visit Windows for SGRQ and UCSD SOBQ

Analysis Visit [AVISITN]	Target Day	Analysis Window (scheduled Study Days)
Baseline [0]	*1*	Last valid assessment prior to first intake of randomized study drug (sildenafil/placebo). Generally, it is assumed that measurements referring to the Day 1 (Week 1) visit have been performed before randomized study drug (sildenafil/placebo) was given.
Week 12 [12]	90	One day after first dose of randomized treatment to 135 (85 to 90)
Week 26 [26]	180	136 to 225 (175 to 185)
Week 39 [39]	270	226 to 315 (265 to 275)
Week 52 [52]	365	316 to maximum of 392
Early discontinuation [53]	Not applicable	As occurred

4.11 INTERIM ANALYSES

Throughout the study, an external independent Data Monitoring Board (iDMC) will review individual SAE reports and laboratory toxicities. The iDMC will meet regularly (approximately every 3 months) to review safety data (and efficacy, if requested) as described in the iDMC charter and advise on the study conduct.

The iDMC may recommend that the Sponsor stop the study for safety concerns set forth in the iDMC Charter. Additional ad hoc meetings or data review can be requested by the iDMC or Sponsor, if warranted. Additional information is provided in the iDMC Charter.

No formal interim analyses for efficacy are planned.

4.12 BIOMARKER ANALYSES (OPTIONAL)

Genomic, transcriptomic and proteomic profiling of markers associated with the molecular pathways and cellular processes of lung injury and fibrosis will be measured. Certain biomarkers may be differentially expressed in patients with advanced IPF and risk of Group 3 PH on pirfenidone treatment (e.g., possibly cytokines, chemokines and

other cellular and molecular markers of lung injury and fibrosis). The blood biomarker samples may help identify those serum and plasma proteins or blood ribonucleic acid (RNA) biomarkers related to disease progression.

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

5. REFERENCES

Galie N, Humbert M, Vachieryc J-L, et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2015;ehv317 67-119.

Wuyts W, Antoniou KM, Borensztain K, et al. Combination therapy: the future of management for idiopathic pulmonary fibrosis? Lancet Resp Med 2014: 2(11): 933–42.

Simonneau, MD, Gatzoulis MA, Adatia I, et al. Updated Clinical Classification of Pulmonary Hypertension. Journal of the American College of Cardiology 2013;Vol 62, No. 25, Suppl D

Han MK, Bach DS, Hagan PG, Yow E, Flaherty KR, Toews GB, Anstrom KJ, Martinez FJ; IPFnet Investigators. Sildenafi l Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction Han et al. Chest. 2013 Jun;143(6):1699-1708. doi: 10.1378/chest.12-1594.

Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.

Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis. N Engl J Med 2010;363:620-8.

Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;126:746-752.

Hallstrand TS, Boitano LJ, Johnson WC, et al. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005;25:96–103.

Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005;128(4):2393-9.

Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. 2005 Mar;2(1):105-10.

Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil foe treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 2002;360(9337):895-900.

Prewitt LM, Ries AL, Kaplan RM. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. 1998 Mar;113(3):619-24.

Nishimura K, Tsukino M, Hajiro T. Health-related quality of life in patients with chronic obstructive pulmonary disease. 1998 Mar;4(2):107-15.

Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. 1991 Sep;85 Suppl B:25-31; discussion 33-7.

St. George's Respiratory Questionnaire

http://www.healthstatus.sgul.ac.uk/sgrq

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An International Working Group Report. Am J Respir Crit Care Med 2016;194:265–75.

Appendix 1
Schedule of Assessments

	Washout[a]	Screening[b]	Double blind treatment phase										Early Study Withdrawal/ Study Treat. Discontinuation	Follow-Up (FU)	Additional safety FU[i]
Day Week	**-57 to -29**	**28 to -1**	**1 W1**	**22 W3**	**45 W6**	**90 W12**	**135 W19**	**180 W26**	**225 W32**	**270 W39**	**315 W45**	**365 W52**		**393**	**up to 11 months**
(Window, days)			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Informed Consent	X[c]														
Demographic data	X														
Medical History and Baseline Conditions	X	X													
Obtain and Review Historical PFTs, HRCT*, Surgical Lung Biopsy, and RHC		X													
Review Inclusion/Exclusion Criteria	X	X	X												
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight			X					X				X	X	X	
Height			X												
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Day Week	Washout[a] -57 to -29	Screening[b] 28 to -1	Double blind Treatment 1 W1	 22 W3	 45 W6	 90 W12	 135 W19	 180 W26	 225 W32	 270 W39	 315 W45	 365 W52	Early Study Withdrawal/ Study Treat. Discontinuation	Follow-Up 393	Additional safety FU i, up to 11 months
(Window, days)			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Spirometry post broncho-dilator (FVC, FEV1, FEV1/ FVC) [d]		X	X [d1]			X		X		X		X	X		
DLCO [e]		X	X [e1]			X		X		X		X	X		
6MWT and SpO2 (resting, nadir, and end of test) [f]		X	X[f]		X	X		X		X		X	X		
Borg scale		X	X		X	X		X		X		X	X		
WHO Functional Class		X	X	X	X	X	X	X	X	X	X	X	X		
Hematology		X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry		X	X	X	X	X	X	X	X	X	X	X	X		
NT-proBNP, CRP, aldosterone			X			X		X				X	X		
Urinalysis		X	X			X		X				X	X		
Urine Pregnancy Test [g]			X	X	X	X	X	X	X	X	X	X	X		

	Washout[a]	Screening[b]	Double blind Treatment										Early Study Withdrawal/ Study Treat. Discontinuation	Follow-Up	Additional safety FU [i], up to 11 months
Day Week	**-57 to -29**	**28 to -1**	**1 W1**	**22 W3**	**45 W6**	**90 W12**	**135 W19**	**180 W26**	**225 W32**	**270 W39**	**315 W45**	**365 W52**		**393**	
(Window, days			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Serum Pregnancy Test		X												X	
12-lead ECG		X	X					X				X	X		
ECHO		X[h]	X[h1]					X				X	X		
SGRQ			X			X		X		X		X	X		
UCSD SOBQ			X			X		X		X		X	X		
Serum and plasma for optional biomarker assessment		X	X												
Blood PAXgene for optional biomarker assessment		X	X												
Blood for optional DNA biomarker assessment			X												
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	

Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Washout[a]	**Screening[b]**	**Double blind Treatment**										**Early Study Withdrawal/ Study Treat. Discontinuation**	**Follow-Up**	**Additional safety FU [i], up to 11 months**
Day Week	**-57 to -29**	**28 to -1**	**1 W1**	**22 W3**	**45 W6**	**90 W12**	**135 W19**	**180 W26**	**225 W32**	**270 W39**	**315 W45**	**365 W52**		**393**	
(Window, days)			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Review Dosing Adherence			X	X	X	X	X	X	X	X	X	X	X		
Review Patient Diary			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense/ Collect Patient Diary		X											X	X	
Dispense Wallet Card			X												
Pirfenidone treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]
Dispense Sildenafil/ Placebo and Explain Dosing			X	X	X	X	X	X	X	X	X	X			
Collect Unused Sildenafil/ Placebo and Empty Bottles					X	X	X	X	X	X	X	X	X		

6MWT = 6-minute walk test; DLCO = pulmonary diffusion capacity; ECG = electrocardiogram; ECHO = echocardiography; NT-proBNP = N-terminal pro-brain natriuretic peptide; RHC = right-heart catheterization; SGRQ = Saint George's Respiratory Questionnaire; UCSD SOBQ = University of California San Diego Shortness of Breath questionnaire; SpO2 = oxyhemoglobin saturation.

* Collect from randomized patients the most recent HRCTs performed prior to entering the study

[a] Patients taking prohibited medications at the time of consent must, after consent, discontinue the prohibited medications 28 days prior to the start of Screening (Day -57 to -29). If a prohibited medication must be tapered, tapering will be followed by discontinuation, and the discontinuation should last at least 28 days (washout period) before the start of screening. Patients that do not require Washout proceed directly to Screening. In addition, a run-in period will be provided for countries where patients will not be able to take pirfenidone for 12 weeks due to reimbursement issues. After signing the ICF, the 12-week run-in pirfenidone supply will be provided by the Sponsor.

[b] The Screening Period of up to 28 days may comprise one or more visits for the convenience of the patient.

[c] Written informed consent will be obtained prior to any study procedures, either prior to Washout or if not applicable, prior to Screening.

[d] Spirometry will be performed only post-bronchodilator. Reference equations for spirometric indices will be provided in the Procedure Manual.

[d1] Should Spirometry at screening collect all information required at Visit 1 and the patient is eligible and randomized in ≤14 days, the screening Spirometry can be used as baseline

[e] The reported DLCO will be corrected for the current hemoglobin level, using reference equations.

[e1] Should DLCO at screening collect all information required at Visit 1 and the patient is eligible and randomized in ≤14 days, the screening DLCO can be used as baseline

[f] The 6MWT will be performed once at each visit highlighted. At Baseline, it will be performed twice and the better of the two 6MWD values will be reported. Please refer to the 6MWT Procedure Manual.

[g] If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

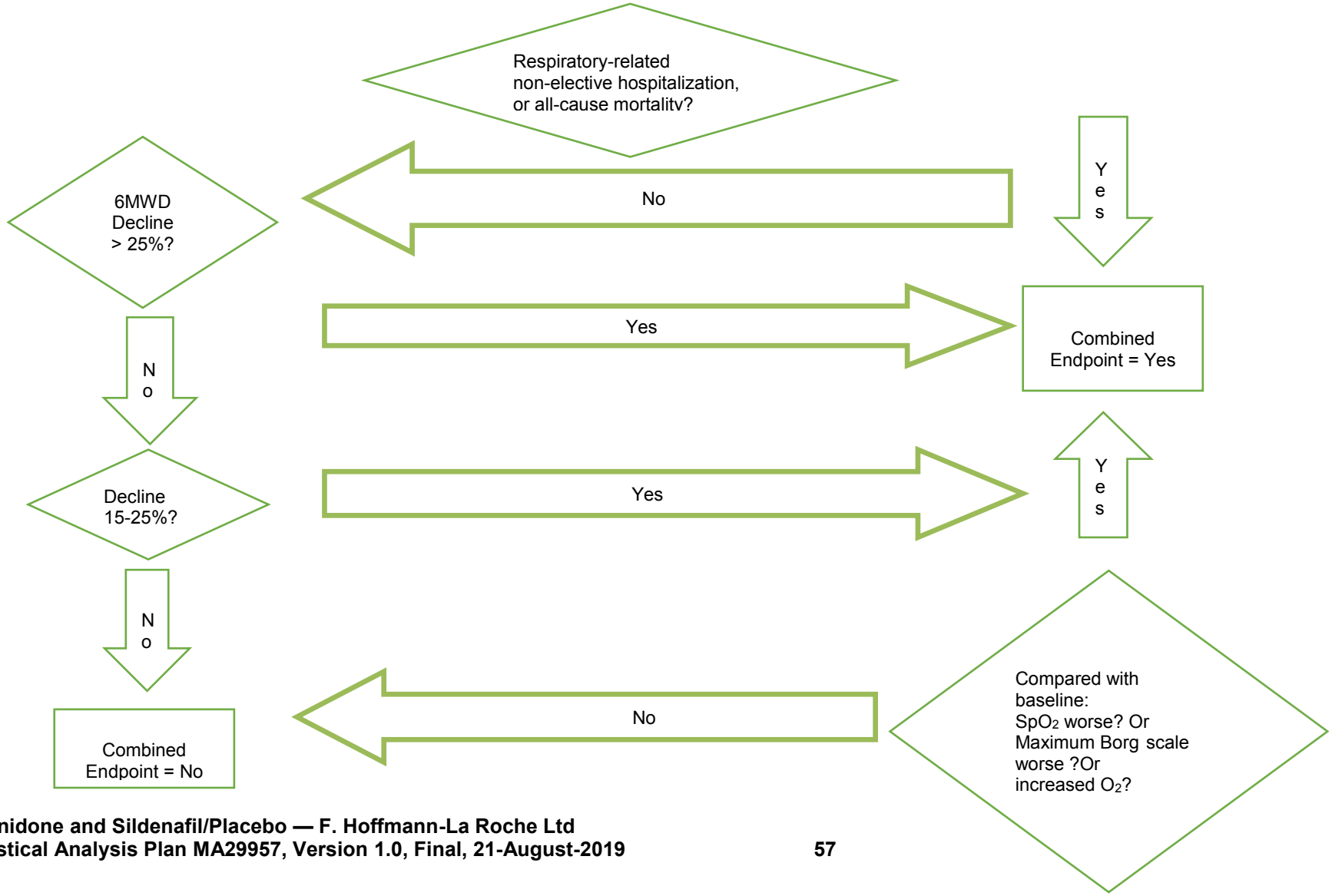
[h] ECHO assessment at screening is not required for eligible patients based on RHC criteria.

[h1] Should the ECHO at screening collect all information required at Visit 1 and the patient is eligible and randomized in ≤14 days, the screening ECHO can be used as baseline

[i] The sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol up to a 11 months safety follow up. During this interval the patients should be evaluated approximately every three months.

[j] During the additional safety FU, data related to the pirfenidone administration will not be collected on the CRF.

Appendix 2
Endpoint Decision process



Appendix 3
MedDRA Browser Basket: Esbriet – Potential Hy's Law AEGT

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

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

Description
AEGT to identify cases of potential Hy's Law: 50 Terms

Created Date	11-May-2016	By User FLOODC
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Included MedDRA Preferred Terms

Liver injury
Bilirubin conjugated increased
Urine bilirubin increased
Hepatobiliary disease
Jaundice
Transaminases abnormal
Subacute hepatic failure
Aspartate aminotransferase increased
Cholestatic liver injury
Bilirubin conjugated abnormal
Mixed liver injury
Hyperbilirubinaemia
Drug-induced liver injury
Hepatic enzyme abnormal
Blood alkaline phosphatase abnormal
Gamma-glutamyltransferase increased
Hepatic failure
Acute hepatic failure
Blood alkaline phosphatase increased
Hepatic enzyme increased
Aspartate aminotransferase abnormal
Biopsy liver abnormal
Liver function test increased
Liver function test abnormal

Blood bilirubin increased
Jaundice hepatocellular
Hepatitis
Alanine aminotransferase abnormal
Hepatitis fulminant
Hepatitis cholestatic
Hepatitis acute
Acute yellow liver atrophy
Cholestasis
Blood bilirubin unconjugated increased
Prothrombin time ratio increased
Chronic hepatitis
Prothrombin time abnormal
Hepatic infiltration eosinophilic
Hepatic function abnormal
Prothrombin time prolonged
Hepatotoxicity
Hepatitis toxic
Transaminases increased
Blood bilirubin abnormal
Prothrombin time ratio abnormal
Liver disorder
Alanine aminotransferase increased
Hepatic necrosis
Gamma-glutamyltransferase abnormal
Hepatocellular injury

MedDRA Version 19.1 used.

Note: The same terms are required for MedDRA version 21.1. They will be reviewed and adapted the higher MedDRA versions.

Appendix 4
Calculation of GAP Index Categories

Calculation of GAP Score

The GAP score and staging system is based on four baseline characteristics, gender, age, %FVC at baseline and %DLco at baseline. If any of the four baseline characteristics is missing then the GAP score is missing.

Table 7 GAP Index and Staging System

	Variable name from ADSL	Predictor	Points
Gender (G)	SEX	Female	0
		Male	1
Age (A)	AGERAND	Age <=60	0
		60<Age=<65	1
		Age >65	2
Physiology (P)	FVCBL	FVC >75	0
		50<=FVC<=75	1
		FVC<50	2
	DLCOBL	DLCO>55	0
		36<=DLCO<=55	1
		DLCO<36	2
		Cannot Perform	3

This definition follows the descriptions used in the Pirfenidone 2014 Resubmission Efficacy Update (RISE).

- GAP Index Stage I: Total Points: 0 to 3
- GAP Index Stage II: Total Points: 4 to 5
- GAP Index Stage III: Total Points: 6 to 8

In order to prevent possible issues with unexpected data formats, the following changes to the above definitions will be performed in this study:

	Variable name from ADIESL	Predictor	Points
Age (A)	AGERAND	Age < 61	0
		61<=Age=<65	1
		Age >65	2

Appendix 5
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.

Appendix 6
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.

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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USA / English version
«Past three months» version

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 <u>these days.</u>

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

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

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.

Appendix 7
Scoring Algorithm: SGRQ

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 walking 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 PATIENTS

Means (95% confidence intervals) for SGRQ scores in normal patients 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 method which 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).

Appendix 8
Acute exacerbations

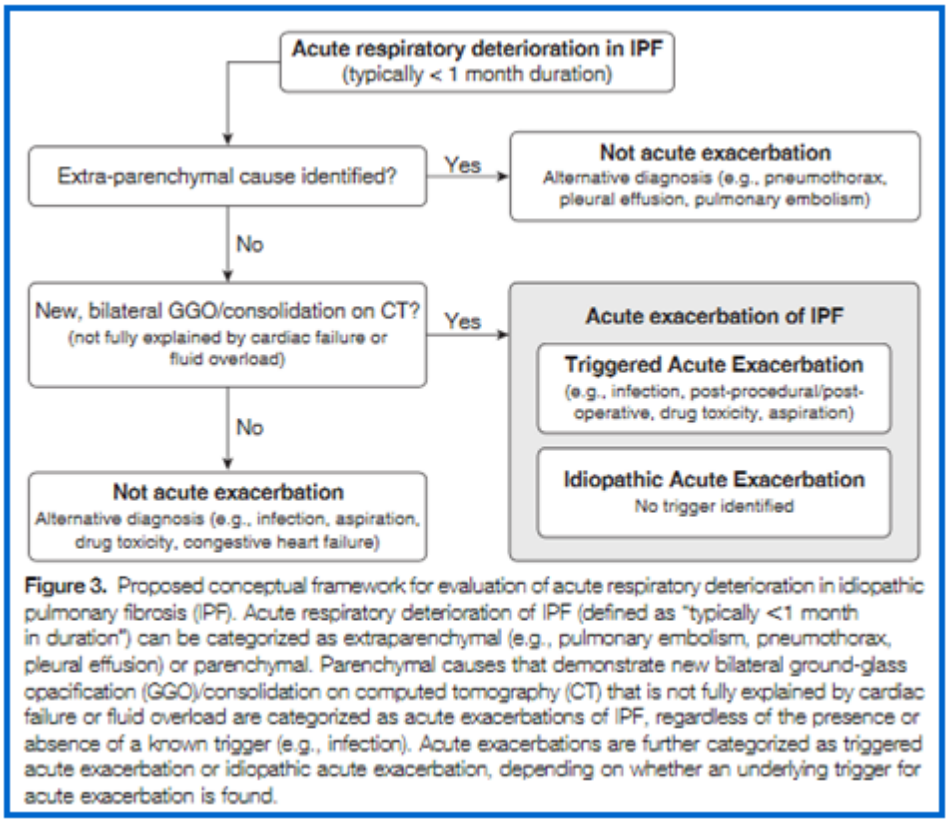

Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification (GGO)/consolidation on computed tomography (CT) that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found.