**Official Title:** **AN INTERNATIONAL STUDY TO CHARACTERISE THE DISEASE BEHAVIOUR OF IDIOPATHIC PULMONARY FIBROSIS AND INTERSTITIAL LUNG DISEASE DURING THE PERI-DIAGNOSTIC PERIOD**

**NCT Number:** NCT03261037

**Document Date:** SAP Version 2: 11-April-2019

| STATISTICAL ANALYSIS PLAN | |
|---|---|
| **TITLE:** | **AN INTERNATIONAL STUDY TO CHARACTERIZE THE DISEASE BEHAVIOUR OF IDIOPATHIC PULMONARY FIBROSIS AND INTERSTITIAL LUNG DISEASE DURING THE PERI-DIAGNOSTIC PERIOD** |
| **PROTOCOL NUMBER:** | **MA39297** |
| **STUDY DRUG:** | **N/A** |
| **VERSION NUMBER:** | **Final Version 2.0** |
| **IND NUMBER:** | **N/A** |
| **Eudract Number:** | **2016-005114-22** |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **PLAN PREPARED BY:** | [redacted] (Clinipace Worldwide (Accovion GmbH))<br>[redacted] (F. Hoffmann-La Roche Ltd) |
| **DATE FINAL:** | 11-Apr-2019 |

## SIGNATURE PAGE

Roche Biostatistician [redacted]

[redacted]
Signature

11.04.2019
Date

Study Biostatistician [redacted]

[redacted]
Signature

11-04-2019
Date

[redacted] [redacted]

[redacted]
Signature

11.04.2019
Date

## STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

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

| Version | Date | Change number | Change description |
|---|---|---|---|
| 2 | 04-Apr-2018 | 1 | Based on the Steering Committee (SC) feedback several specifications on home spirometry data were included in the section Primary Outcome Measures. |
| 2 | 04-Apr-2018 | 2 | Some updates are presented under section Secondary Outcome Measures to clarify, for example, the derivation of the index utility score for the EQ-5D questionnaire. |
| 2 | 04-Apr-2018 | 3 | Selected listings and tables to be presented were specified in the section Statistical Methods. In addition, baseline definitions for site and home measurements were included. |
| 2 | 04-Apr-2018 | 4 | Further subgroups were specified in section Subgroups. |
| 2 | 04-Apr-2018 | 5 | Additional IPF/ILD diagnosis analyses and further clarifications according the the latest version of the eCRF were included in section IPF/ILD diagnosis. |
| 2 | 04-Apr-2018 | 6 | Additional analyses on the number of patients that decided to see/continue to see his/her information on daily lung function and physical activity level is included under section Home measurements. |
| 2 | 04-Apr-2018 | 7 | Additional figures are presented under section Compliance for presenting the non-compliance of the home daily measurements in a bar plot. |
| 2 | 04-Apr-2018 | 8 | Primary endpoint analyses were detailed under section Primary Endpoints where additional figures needed where specified. |
| 2 | 04-Apr-2018 | 9 | Secondary endpoint analyses were detailed under section Secondary Endpoints where several additional outputs were included as: correlation between home and site measurements for spirometry and accelerometry, gap score analysis, etc. |
| 2 | 04-Apr-2018 | 10 | Exploratory analyses, sensitivity analyses and subgroup analyses were specified under sections Exploratory Endpoints, Sensitivity Analyses and Subgroup Analyses. |
| 2 | 04-Apr-2018 | 11 | Related to safety analyses, modifications were needed to clarify the definition of acute exacerbations, the period of the events related to the study assessments and the definitions of previous, concomitant and post medications (Safety Analyses) |
| 2 | 04-Apr-2018 | 12 | Interim analysis section was updated to better specify the objective and timelines of the several interim analysis needed for the study: Interim Analyses |

| | | | |
|---|---|---|---|
| 2 | 04-Apr-2018 | 13 | Missing data rules were modified to not taking into account the prior flag collected in the eCRF but just the dates: Missing Data. |
| 2 | 04-Apr-2018 | 14 | References and several clarifying appendix were included at the end of the document. |

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF APPENDICES

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 6MWD | 6-minute walk distance |
| ANCOVA | analysis of covariance |
| BAL | Bronchoalveolar lavage |
| BP | blood pressure |
| CI | confidence interval |
| CRO | contract research organization |
| CTP | Clinical Trial Protocol |
| DLco | diffusing capacity of the lung for carbon monoxide |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EQ-5D-5L | The EuroQol 5-Dimension Questionnaire |
| ERS | European Respiratory Society |
| FAS | Fatigue Assessment Scale |
| FDA | Food and Drug Administration |
| FEV1 | forced expiratory volume in 1 second |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| HRCT | high-resolution computed tomography |
| HP | Hypersensitivity pneumonitis |
| IA | Interim Analysis |
| IMP | Investigational medicinal product |
| IPF | Idiopathic pulmonary fibrosis |
| ICH | International Conference on Harmonisation |
| ILD | interstitial lung disease |
| K-BILD | King's Brief Interstitial Lung Disease Questionnaire |
| LoPO | List of planned outputs |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mMRC | Modified Medical Research Council Dyspnea Scale |
| PFTs | pulmonary function tests |
| PT | Preferred term |
| PRO | patient-reported outcome |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| SC | Steering Committee |
| SOC | System Organ Class |
| SPD | Steps per day |
| SpO2 | oxyhemoglobin saturation at rest |
| TMS | Trial Management System |
| uILD | Unclassifiable ILD |
| UIP | Usual interstitial pneumonia |
| VAS | Visual Analogue Scale |

# 1. BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the radiologic and/or histopathologic pattern of usual interstitial pneumonia (UIP). The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and interstitial lung disease (ILD) associated with environmental exposure, medication, or systemic disease (American Thoracic Society and European Respiratory Society 2002).

The classification of interstitial lung diseases (ILDs) requires multidisciplinary expertise with input from various clinical experts, including pulmonologists, thoracic radiologists, and lung pathologists (Ryerson and Collard 2013).

Symptoms of IPF have usually been present for at least 6 months before the diagnosis is made. The initial clinical presentation is typically that of slowly progressive dyspnea and nonproductive cough. Digital clubbing occurs in up to 50% of patients. Lung auscultation reveals fine end inspiratory crackles, initially at the base of the lung and ultimately diffusely (Raghu et al. 2011). In advanced disease, features of right heart failure develop. Pulmonary function tests demonstrate a restrictive pattern, with a decrease in carbon monoxide diffusing capacity ($DL_{CO}$), and oxygen desaturation on exertion. Chest radiographs show diffuse interstitial opacities with volume loss, and high-resolution computed tomography (HRCT) scans show a characteristic pattern of peripheral (subpleural), bibasilar, reticulonodular abnormalities associated with architectural distortion, honeycomb changes, and traction bronchiectasis (Raghu et al. 2011, Raghu et al. 2018).

The diagnosis of IPF carries a bleak prognosis, with progressive disability due to respiratory insufficiency (Hallstrand et al. 2005). Data from the placebo arm of several controlled clinical trials suggest that the rate of decline in forced vital capacity (FVC) in patients with IPF is approximately 150 to 200 mL/yr in patients with IPF (Demedts et al. 2005; Ley et al. 2011; Raghu et al. 2004, 2008). Estimated survival, in the absence of treatment, is between three to five years after diagnosis (American Thoracic Society and European Respiratory Society 2002; Bjoraker et al. 1998; Douglas et al. 2000; Gribbin et al. 2006; Hyldgaard et al. 2014; Kim et al. 2006; Mapel et al. 1998; Olson et al. 2007).

A diminished quality of life in patients with IPF is well established, with impaired energy level and decreased level of independence in concert with respiratory symptoms (Swigris et al. 2005).

To date, two anti-fibrotic drugs have been approved for use in IPF: pirfenidone and nintedanib; both therapies have shown to significantly slow the progression of lung function decline in IPF (Raghu et al. 2015), although the disease remains incurable.

In terms of current clinical practice, there are limited data available on the early course of disease in symptomatic patients with suspicion of IPF/ILD. Thus, the peri-diagnosis period (see definition in Section 2.2) including the pre- and post-diagnosis periods is critical to the assessment of disease behavior, the timely accurate diagnosis and the decision to treat. The study will not focus on asymptomatic stages of disease when discovery would rely on imaging techniques for lung cancer screening purposes or incidental finding.

This study will characterize the disease behavior of IPF and ILD patient in the peri-diagnostic period, having as aim to increase the knowledge of the progressive nature of IPF/ILD already at early phases of assessment.

This objective will be achieved using a multidimensional approach assessing changes in pulmonary function, measured by daily handheld spirometry as well as assessing physical functional capacity.

# 2. STUDY DESIGN

## 2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1and the Schedule of Assessments in Appendix 2. For additional details, please see the Protocol Version 1, 26 April 2017 (and its Appendices).

## 2.2 OUTCOME MEASURES

By use of different outcome measures, a primary and multiple secondary and exploratory objectives will be investigated.

The primary objective of the study is to characterize the disease behavior of IPF during the peri-diagnostic period, where the peri-diagnostic period covers:

- the pre-diagnosis period (from inclusion into the study to diagnosis; for a maximum of 12 months).
- the post-diagnosis period (from the diagnosis to the start of drug treatment within 6 months or a maximum of 6 months after diagnosis if no treatment is started).

The investigation of the primary objective is based on Forced Vital Capacity (FVC) measurements in mL by daily home spirometry.

Secondary objectives of the trial are:

- to characterize the disease behavior of non-IPF ILD during the peri-diagnostic period. This will be based on the investigation of FVC measurements in mL by daily home spirometry.
- to further characterize the disease behavior of IPF and non-IPF ILD in the peri-diagnostic period using a multidimensional approach. Hereby, a set of outcome measures will be used, which will be described in detail in the following sections.

Exploratory objectives of the trial are:

- Characterization of different subgroups
- Evaluation of the differences in FVC values at beginning of treatment, depending on reimbursement restrictions
- Evaluation of the collaboration platform
- Evaluation of the digital solution set up for the patients

Please note that the exploratory objective to evaluate the differences in FVC values at the beginning of treatment, depending on reimbursement restrictions as described in the CTP may be omitted in case that no countries with reimbursement restrictions will actually be taking part in the trial.

### 2.2.1 Primary Outcome Measures

Throughout the study, patients should perform a spirometry measurement of FVC [mL] at approximately the same time each day. For this purpose, study participants will be provided with a portable handheld spirometer and a tablet computer. Each spirometer will be factory calibrated.

The primary outcome measure is pulmonary function by use of FVC measurements in mL by daily home spirometry.

Note that for every FVC measurement the quality of the manoeuvre is monitored and documented according to acceptability criteria shown in the flow chart of Appendix 3 . Depending on different characteristics of the blow, quality criteria will be provided to the patient and documented with the measurement (e.g. “blow out faster”, “blow out longer”).

Table 1 shows which of the quality criteria are considered acceptable and not acceptable manoeuvres.

Based on the Steering Committee (SC) feedback and in order to exclude the potential learning curve of each patient, the first 7 days of measurements per patient will be

removed from the analyses. All measurements will be taken into account for the analyses in case we have more than 1 per day.

**Table 1 Quality criteria for FVC measurements**

| Not acceptable manoeuvre | Acceptable manoeuvre |
|---|---|
| • Blow out faster<br>• Blow out longer<br>• Abrupt end | • Don't start too early<br>• Avoid coughing<br>• Good blow |

For analysis purpose only non-test acceptable manoeuvres flagged as 'Good blow' will be considered. In addition, any data point collected by the device before enrollment visit and after EOS visit, respectively, will be excluded from the analysis. In case a patient received treatment before EOS visit all data after treatment start date (inclusive site spirometry etc.) will be excluded from analysis as well. In order to consider only data points that are clinically meaningful FVC values outside a range from 400 ml to 6000 ml will also be excluded from analysis.

The corresponding primary endpoint used for the investigation of disease behavior of IPF is defined as the time-adjusted semi-annual FVC decline in patients with IPF during the peri-diagnosis period. Please refer to Section 4.5.1 for a detailed description of statistical analysis which is used for the computation of the primary endpoint.

### 2.2.2 Secondary Outcome Measures

#### 2.2.2.1 FVC measurements

Additionally, to the daily spirometry measurements by the patients, FVC [mL] and in % predicted values should be assessed by site spirometry at every visit.

#### 2.2.2.2 Physical function capacity

Patients will be asked to wear an accelerometer during the course of the study which provides information on their physical activity, such as steps per day and calorie expenditure. These daily measurements will be used to investigate the development of physical function capacity over time. The first 7 days of measurements per patient will be removed from the analyses as done with spirometry home data. In addition, any data point collected before enrollment visit up to start of treatment or EOS visit whatever occurred first will be deleted and for steps per day (SPD) a range for acceptable values from 200 to 20000 will be applied.

#### 2.2.2.3 6MWT

The 6MWT measures the distance a patient is able to walk quickly on a flat, hard surface in a period of 6 minutes.

The 6MWT should be conducted at each patient visit, only at sites where a formalized process is available and the test can be performed under safe conditions.

#### 2.2.2.4 Patient-Reported Outcomes (PRO)

Various paper-based PRO questionnaires and visual analog scales (VAS) will be used to monitor the patients' health status and well-being during the study.

- **King's Brief Interstitial Lung Disease (K-BILD) Questionnaire**

  This questionnaire was specifically developed to analyze the health status of patients with ILD. The questionnaire consists of 15 items that have to be assessed by the patients on a scale ranging from 1 to 7, where 1 and 7 represent worst and best health status, respectively.

  Items are compiled into three domains: breathlessness and activities, psychological, and chest symptoms. A detailed description how the total score and the domain scores are calculated can be found in Appendix 4.

- **Modified Medical Research Council (mMRC) Dyspnea Scale**

  The mMRC dyspnea scale is simple to administer and has been used for many years to grade the effects of breathlessness on daily activities. Grading will be done according to the following categories:

| | |
|---|---|
| Grade 0 | I only get breathless with strenuous exercise |
| Grade 1 | I get short of breath when hurrying on the level or walking up a slight hill |
| Grade 2 | I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking on my own pace |
| Grade 3 | I stop for breath after walking about 100 yards or after a few minutes on level ground |
| Grade 4 | I am too breathless to leave the house |

- **The EuroQol 5-Dimension Questionnaire (EQ-5D-5L)**

The 5-level version is a validated self-report health status questionnaire with two components:

- A five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item is rated by the patient on a five-point scale where
    - Level 1: indicating no problem
    - Level 2: indicating slight problems
    - Level 3: indicating moderate problems
    - Level 4: indicating severe problems
    - Level 5: indicating extreme problems
- A unique health state is defined for each patient by combining the levels from each of the 5 dimensions. A total of 3125 possible health state profiles is defined in this way. Each state is referred to in terms of a 5 digit code, e.g. state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with usual activities, severe pain or discomfort and extreme anxiety or depression. The health state of each patient can be converted into a single index value, presented by country specific value sets. SAS code including the respective index values for each of the possible 3125 health states for each country is available in order to convert health state profiles of each patient into index values as described above. Please note that an index value can only be derived in case ratings for all 5 dimensions are available. If for a patient a rating of one or more dimensions is missing, the index value is missing, too.
- A VAS that measures health state. The VAS is a 100 mm scale from worst (0 mm) to best (100 mm) health the patient can imagine.

For further information related to the EQ-5D-5L questionnaire, please refer to Appendix 7.

- **Fatigue Assessment Scale (FAS)**

The FAS is a fatigue questionnaire consisting of 10 items; five questions reflect physical fatigue and five questions analyze mental fatigue. A five-point scale (one for “never” to five for “always”) is used for patient responses. The scale score is calculated by summing all items. Therefore, the FAS scores can range from 10 to 50.

- **Cough / Urge to cough / Fatigue Visual Analogue Scales (VAS)**

  The VAS are 100 mm scales on which patients indicate the severity of their cough, the urge to cough and their fatigue.

By use of the described secondary efficacy outcome measures the following secondary endpoints are defined and investigated:

- Change in pulmonary function tests from baseline (FVC measured in mL by daily home spirometry) for each diagnosis cohort.
- Change in pulmonary function tests from baseline (mL and % predicted FVC) by site spirometry for each diagnosis cohort
- Change in 6MWT from baseline over time for each diagnosis cohort
- Change in physical functional capacity (measured by daily home accelerometry, e.g. number of footsteps per day) from baseline over time for each diagnosis cohort
- Change in PRO measures from enrollment visit to diagnosis visit and EOS visit as well as change from diagnosis visit to EOS visit over time will be summarized for each diagnosis cohort.

### 2.2.3 Exploratory Outcome Measures

The following exploratory efficacy outcome measures will be documented by use of additional questionnaires:

- Evaluation of the collaboration platform by Investigators
- Evaluation of the digital solution set up for patients

### 2.2.4 Safety Outcome Measures

This study has no protocol mandated investigational medicinal product (IMP) or treatment requirements. Patients will stop the study prior to starting any drug treatment for IPF/ILD.

Any occurrence of non-elective hospitalization, Investigator-reported acute exacerbations, deaths, and events related to study assessments will be collected in the eCRF only.

Any untoward occurrences thought to be due to, or associated with, a commercial medicinal product used during the course of a patient's standard medical treatment will not be reported in the eCRFs, but should be reported to the respective Market Authorization Holder or local Health Authority according to local regulatory requirements.

## 2.3 DETERMINATION OF SAMPLE SIZE

The main purpose of this study is hypothesis generation and estimation regarding the impact on pulmonary function in terms of the change in FVC, as measured by daily handheld spirometry, in patients suspected to suffer from IPF.

For this study, a total sample size of approximately 180 patients was planned (Table 2). The majority of the patients will be enrolled into two study cohorts, i.e., patients with a diagnosis of IPF or non-IPF ILD. Due to the uncertainty of the numbers of patients to be enrolled into these two cohorts, the sample size could not be derived for a certain patient number. For the purpose of sample size and power calculation, it was assumed that approximately 40% of patients will be diagnosed with IPF and 50% of patients will be diagnosed with non-IPF ILD. Approximately 10% of patients were expected to suffer from a disease other than ILD (non-ILD) or were expected not have a diagnosis within 12 months of enrollment. This assumption was based on published data (Wapenaar-deKorver et al. 2016).

Thus, it was expected to enroll approx. 72 patients with a diagnosis of IPF and approx. 90 patients with a diagnosis of non-IPF ILD. Approximately 18 patients may be diagnosed with non-ILD or have no diagnosis within the 12 months period following enrollment.

**Table 2 Sample Size Scenarios**

| Number of patients with IPF | Mean FVC decline [mL] over 6 months | Lower Bound of 95% CI | Upper Bound of 95% CI | Total number of patients to be enrolled |
|---|---|---|---|---|
| 72 | 25 | 8.83 | 41.17 | 180 |
| 72 | 50 | 33.83 | 66.17 | 180 |
| 72 | 75 | 58.83 | 91.17 | 180 |

CI = confidence interval

In Table 2 point estimates and 95% confidence intervals based on a normal distribution are tabulated for a range of possible outcomes, assuming 72 patients

analyzed, a standard deviation of 70 ml, and a precision of 16.17% (estimates produced using nQuery, version 7). A mean semi-annual FVC decline in the IPF group of 50 mL was considered to be a clinically relevant decline and a reasonable expectation in accordance with the literature (Ley et al. 2011). In addition, after inspection of historical data, it could be assumed that the common standard deviation in mean FVC decline was 70 mL as measured by handheld spirometry.

# 3. STUDY CONDUCT

The study conduct is described in Section 2.

## 3.1 RANDOMIZATION, BLINDING AND UNBLINDING PROCEDURES

Not applicable.

## 3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

## 3.3 DATA MONITORING

Not applicable.

# 4. STATISTICAL METHODS

Categorical data will be summarized using frequencies and percentages (including a category for missing, if appropriate). Percentages will be based on the number of patients in each diagnosis cohort (a definition of different diagnosis cohorts is provided in Section 4.2.2), if not otherwise specified.

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

Where applicable other analysis methods will be specified below.

## 4.1 ANALYSIS POPULATIONS

No analysis populations are defined in this trial. Data of all enrolled patients will be analyzed (enrolled patients have signed informed consent and passed all in- and exclusion criteria) by diagnosis cohorts, if possible.

Following thorough assessments and diagnoses, four groups of patients will be identified and allocated to one of the following diagnosis cohorts:

- Patients diagnosed with IPF (IPF patients)
- Patients diagnosed with an ILD other than IPF (non-IPF ILD patients)

- Patients diagnosed with a condition that is not an ILD (non-ILD patients)
- Patients without diagnosis after 12 months assessments

## 4.2 TRIAL PERIODS, OBSERVATION AND ANALYSIS TIMES

The study consists of the peri-diagnosis period (from enrollment until end of study visit), which is divided into a pre- and post-diagnosis period (please refer to Sections 4.2.3 and 4.2.4 for the definition of these periods). Site visits will be conducted at a minimum at baseline, diagnosis, and end-of-study for each individual patient. During each study period, every patient should have at least one site visit, scheduled at the discretion of the investigator.

All patients will be managed at the discretion of the Investigator taking into account local clinical practice guidelines and standards of care as well as available clinical evidence for patients with suspected IPF/ILD or diagnosed with IPF/ILD.

### 4.2.1 Study Days

Study day is defined as the number of days since day of enrollment (Enrollment visit), i.e. Study day = Assessment date – date of enrollment + 1.

### 4.2.2 Baseline Observations

After discussion of the results of the first interim analysis from December 2018 with the SC in January 2019 it was decided to re-define the calculation for baseline FVC from home spirometry and steps per day from accelerometry. This new definition is given in Table 2 below.

**Table 2 Definition of Baseline Observations**

| | Definition |
|---|---|
| Baseline data for site visit measurements | Baseline is defined as the measurement collected at the enrollment visit of each assessment. |
| Baseline data for home measurements | Baseline is defined as the average of the daily measurements collected during the next 7 consecutive days after the first 7 days removed, counted from the day of the first acceptable manoeuvre flagged as 'Good blow' of home spirometry after enrollment visit as defined in Table 1. |

### 4.2.3 Pre-diagnosis Assessment Period

From inclusion into the study (enrollment visit), patients will be followed for a maximum of 12 months in the pre-diagnosis assessment period. The length of the pre-diagnosis period will be derived as follows:

Pre-diagnosis period = date of diagnosis – date of enrollment visit + 1
or = date of end of study visit – date of enrollment visit + 1

where diagnosis date is taken from the IPF/ILD diagnosis eCRF page.

In case the diagnosis date and/or end of study visit is missing and no diagnosis is documented for the patient, the pre-diagnosis period will be set to the maximum of 12 months.

### 4.2.4 Post-diagnosis Assessment Period

Patients diagnosed with IPF or non-IPF ILD at Visit 2 will remain and be followed in the study up to the start of drug treatment (within 6 months) or a maximum of 6 months if no drug treatment is prescribed.

“Start of drug treatment” is defined as the date the treatment is planned to commences. This includes the event of a patient receiving IPF or ILD drug treatment from a physician other than the investigator.

The length of the post-diagnosis period is thus defined as:

Post-diagnosis period = date of start of drug treatment – date of initial diagnosis or
= date of end of study visit – date of initial diagnosis

whichever comes first, where diagnosis date is taken from the IPF/ILD diagnosis eCRF page. In addition, any data point collected after initiation of treatment until EOS visit will be excluded from any analysis.

### 4.2.5 End of Study

For individual patients, the end of the study will be as follows:

- Should no diagnosis be made 12 months after inclusion into the study, the patient will leave the study and perform the end of study visit
- Patients diagnosed with a non-ILD condition will leave the study on the date of diagnosis

- Patients diagnosed with IPF or non-IPF ILD will remain in the study and be followed up to the start of drug treatment (within six months) or a maximum of six months if no drug treatment is prescribed

## 4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Not applicable.

## 4.4 ANALYSIS OF STUDY CONDUCT

### 4.4.1 Patient Disposition

An overview on patient disposition, showing number and percentages of patients screened (patients who have signed informed consent), screening failures, patients enrolled, patients who completed the study at the end of pre-diagnosis or post-diagnosis period, patients with and without start of treatment and patients that prematurely discontinued the study will be provided by diagnosis cohorts and separately by country and center. Centers are thereby classified into “community sites” and “tertiary sites”. An actual list of sites with the allocation to “community” and “tertiary” can be found on Appendix 5. For patients who discontinued the study prematurely, frequencies of reasons for early discontinuation will be provided. In addition, a listing specifying the patient disposition status and reasons for early discontinuation will be presented.

### 4.4.2 Major Protocol Deviations

The Investigator should document and explain any protocol deviation. The Investigator should promptly report any deviation that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

A table summarizing major protocol deviations will be provided by diagnosis cohorts, and protocol deviations will be also listed.

### 4.4.3 Demographic and Baseline Characteristics

Baseline and disease characteristics such as demographics, female reproductive status, tobacco and alcohol use history, and medical history and baseline conditions assessment will be summarized by descriptive statistics or frequency tables. Tables will be displayed by the different diagnosis cohorts. Moreover, demographic and baseline characteristics listing will be presented.

#### 4.4.3.1 Demographics

The following demographic characteristics will be summarized:

- Age (years): date of birth – date of enrollment visit, and age categories (18-64; 65-84; >=85 years)
- Gender
- Race (in case that more than one race will be ticked, a concatenated variable, containing all races will be presented (e.g. Asian/White))
- Ethnicity
- Weight, height and Body Mass Index (BMI) = weight(kg)/height(m)$^2$
- Female reproductive status
- Tobacco use history and nicotine exposure
- Alcohol use history and alcohol consumption, that will be presented only in the final analysis.
- Home spirometry and accelerometry : FVC (mL) and steps per day.

#### 4.4.3.2 Medical History

Medical history and baseline conditions assessments will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 21.1 or above and will be listed and summarized presenting numbers and frequencies by primary System Organ Class (SOC) and Preferred Term (PT) by diagnosis cohorts. If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

#### 4.4.3.3 Subgroups

In addition, an overview table displaying the number of patients of the different subgroups that are used to investigate exploratory objectives will be given. The table includes the following subgroups:

- Patients from community/tertiary sites
- Countries involved in the study
- Patients with/without post-diagnosis period
- Patients with/without at least 3 months of observation time from first day after the time window for calculation of baseline from home spirometry until EOS

- Patients having/not having at least one lung biopsy

- Progressing/non-progressing patients: progressing patients are characterized by a semi-annual decline in FVC of > 50 ml (using home-based spirometry measurements) and/or >15% decline (absolute difference) in steps/day at the end of the study compared to baseline. The average of the last 7 days measurements will be compared with baseline (defined in Section 4.2.2). Patients not fulfilling these requirements are defined as non-progressing patients. Data up to the end of study visit will be used for the assignment of progressing/non-progressing patients in order to compare the semi-annual FVC decline and steps/day during the whole peri-diagnosis period.

- Patients requiring/not requiring at least one respiratory-related hospitalization (as documented by the investigator in the eCRF)

- ILD subgroups: for non-IPF ILD patients ILD subgroups are defined based on types of ILD as ticked by the investigator in the eCRF, i.e.

    - Collagen = ILD of known causes – Collagen

    - HP = HP (hypersensitivity pneumonitis)

    - NSIP = Idiopathic NSIP: Non-specific interstitial pneumonia

    - uILD = uILD (Unclassifiable ILD)

    - Other = all other types of ILD

In addition to the described baseline characteristics there are several patient population characteristics that are assessed during or at the end of the peri-diagnosis period. These assessments will therefore be analyzed as post-baseline characteristics.

#### 4.4.3.4 IPF/ILD diagnosis

A listing and a frequency table will be provided for IPF and non-IPF ILD patients displaying details of the diagnosis (e.g. types of ILD, assessments used for diagnosis). In addition, information from working diagnosis for non-diagnosed patients will be tabulated and listed. Additionally, a Kaplan-Meier analysis is performed with respect to the time from enrollment to diagnosis, the time from enrollment to start of treatment, and time from diagnosis to start of treatment (for IPF and non-IPF ILD patients), presenting summary tables and corresponding KM plots separately by cohort. Thereby, the following rules for censoring will be applied:

- Time from enrollment to diagnosis (in weeks):

Only diagnosed patients will be analyzed separately by cohort. For that reason, there will be no censoring observations.

- Time from enrollment to start of treatment (in weeks):

  If a patient was diagnosed and did not start IPF/ILD treatment during the post-diagnosis period or is lost to follow-up, the patient will be censored at the time of the end of study visit, or at the last available visit during the post-diagnosis period. Frequencies of patients with events and without events, i.e. that treatment was initiated or not, will be presented together with the KM estimates.

- Time from diagnosis to start of treatment (in weeks):

  If a patient was diagnosed and did not start IPF/ILD treatment during the post-diagnosis period or is lost to follow-up, the patient will be censored at the time of the end of study visit, or at the last available visit during the post-diagnosis period. Frequencies of patients with events and without events, i.e. that treatment was initiated or not, will be presented together with the KM estimates.

The duration of pre- and post-diagnosis periods is analyzed by use of a summary table.

### 4.4.4 Disease relevant optional assessments

Investigators can indicate whether disease relevant optional assessments have been performed for the patients, i.e. ECHO, Radiography, Bronchoalveolar lavage (BAL), BNP/NT-proBNP, high-resolution computed tomography (HRCT), lung biopsy or DLco assessment. A frequency table displaying the number of patients with optional assessments will be provided by diagnosis cohort. For results of optional assessments summary, frequency tables will be provided by diagnosis cohorts as appropriate.

### 4.4.5 Home measurements

A summary table over time will be presented to include the number of patients that chosen to see/continue to see his/her information on daily lung function and physical activity level.

### 4.4.6 Compliance

With respect to the home-based daily measurements compliance of patients will be investigated. It will be analyzed if gaps of measurements occur over time. A gap is thereby defined as 7 or more than 7 consecutive days of missing measurements and they are collected in the eCRF. A summary table displaying number of patients with gaps in daily measurements, number of gaps per patient (from 1 to the maximum number of gaps per patient) and duration of gaps will be provided by diagnosis cohorts for data from handheld spirometer and accelerometer. In addition, a bar plot will be

provided for spirometry and accelerometry data by cohort (IPF, non-IPF ILD, patients not diagnosed) specifying the daily data per patient and the number of gaps as collected in Cyberfish. All gaps will be included in the bar plot, even if they are of less than 7 consecutive days. The diagnosis date by patient will be also specified in the bar plot.

## 4.5 EFFICACY ANALYSIS

Generally, daily measurements by the patients are analyzed separately for the peri-diagnosis, pre-diagnosis and post-diagnosis periods (please refer to Section 4.2 for definition of periods). For the peri- and post-diagnosis period only IPF and non-IPF ILD patients are taken into account (since non-ILD patients and patients without diagnosis complete the trial at the end of the pre-diagnosis period). All measurements performed during site visits will be analyzed over the peri-diagnosis period only.

### 4.5.1 Primary Endpoints

The primary endpoint of the study is the time-adjusted semi-annual mean FVC decline (mL) in patients with IPF during the peri-diagnosis period (see Section 4.2) estimated from daily home spirometry measurements.

The semi-annual mean FVC decline is calculated by use of the estimated semi-annual FVC decline of each individual patient. The individual FVC decline is thereby estimated by applying a linear regression model to all acceptable FVC measurements flagged as 'Good blow' according to the MIR criteria (please refer to Section 2.2.1 for the definition of acceptable measurements) collected by the individual patient during the entire peri-diagnosis period, i.e.

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

where

$X_{it}$ = the FVC measurements (mL) of patient i on day t, with i=1,…,N and t=1,…,T

$D_{it}$ = study day t of patient i

$\alpha_i, \beta_i$ = intercept and slope of the individual linear regression of patient i

The time-adjusted semi-annual decline for patient i is then obtained by estimating the patients' individual difference in predicted values between baseline (study day 0) and study day 183 from the linear regression:

$$\widehat{\Delta X}_{i,183} = \widehat{\beta}_i * 183$$

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

A summary table displaying the semi-annual mean FVC decline during the peri-diagnosis period together with two-sided 95% confidence intervals based on percentiles of the t-distribution will be provided for IPF patients (primary analysis) and non-IPF ILD patients (secondary analysis). The same table is also provided for patients of all diagnosis cohorts for the pre-diagnosis period at 3, 6 and 12 months.

Further sensitivity analyses are specified under Section 4.5.4.

A table displaying parameter estimates for the different diagnosis cohorts together with 95% confidence intervals and expected semi-annual and annual FVC values will be provided.

In order to investigate the individual development of home-based measured FVC values individual plots of the FVC values over time will be provided including the regression line and all quality blows with different colors, presenting a blue color for “Good Blows”, green color for “Don’t Start Too Early” manouvre, red color for “Avoid Coughing” manouvre. The diagnosis date will be presented in the plots with a vertical line.

### 4.5.2 Secondary Endpoints

The change in pulmonary function tests (FVC measured in mL by daily home spirometry) in patients with non-IPF ILD will be analyzed in the same way as the primary endpoint (see Section 4.5.1).

The change in FVC (mL and % predicted) measured by site spirometry will be analyzed in the same fashion as the primary endpoint for the peri-diagnosis period only (taking all visits into account). Therefore, these analyses will only be performed for IPF and non-IPF ILD patients. Additionally, a summary table of FVC values measured by site spirometry and changes from baseline will be provided by visit for all diagnosis cohorts (whereas for IPF and non-IPF ILD patients visits of the complete peri-diagnosis period will be displayed in contrast to non-ILD patients and patients without diagnosis where only visits of the pre-diagnosis period are available). In case more than one visit was performed during the pre-/post-diagnosis period, mean FVC values of these visits will be used for the derivation of descriptive statistics.

The correlation of FVC (mL) between home and site spirometry will be analyzed by taking into account the individually estimated linear regression models of each patient for home-based FVC measurements and site FVC measurements. The time-adjusted semi-annual declines for home and site FVC as described for the primary analysis will be

calculated for each patient. Pearson's correlation coefficient of these values will be estimated and displayed within a table. Please note that this analysis will be performed for the peri-diagnosis period only for IPF and non-IPF ILD patients.

The change in 6MWT will be analyzed descriptively over time. A summary table displaying descriptive statistics for Sp02 at rest (%), distance walked (m), Sp02 at the end of the test (%), oxygen requirements (L), and Borg scale and changes from baseline over visits will be displayed by diagnosis cohorts. In case more than one visit was performed during the pre-/post-diagnosis period, mean parameter values of these visits will be used for the derivation of descriptive statistics.

In order to investigate the timely development of physical functional capacity measurements, individual graphs of the number of steps/day by patient will be also provided.

Additionally, the correlation between physical functional capacity assessed at home, i.e. the number of steps per day and on site (distance walked based on the 6MWT), will be analyzed by calculating Pearson's correlation coefficient, analogously to the correlation analysis of home and site spirometry measurements. Please note that this analysis will be performed for the peri-diagnosis period only for IPF and non-IPF ILD patients.

For the K-BILD questionnaire a frequency table of the individual items is provided by visit and diagnosis cohort. Additionally, a summary table of K-BILD total scores and subscores and changes from baseline and from diagnosis is given by visit and diagnosis cohort.

Outcomes and changes over time of the mMRC Dyspnea Scale and for the patient status are analyzed by use of shift tables from baseline and from diagnosis visit over time. Separate tables will be provided for each diagnosis cohort.

GAP score will be presented over time by visit together with the corresponding change from baseline and from diagnosis visit.

For the EQ-5D-5L questionnaire a frequency table displaying outcomes of individual items of the questionnaire will be given by visit and diagnosis cohort. For the index utility score values derived from the individual health state profiles of the EQ-5D-5L and the VAS values, separate summary tables will be provided by visit including changes from baseline and from diagnosis visit over time. In addition, line graphs per cohort will be presented for the EQ-5D-5L index utility score and VAS score.

Summary tables by visit and changes from baseline and from diagnosis visit over time will also be displayed by diagnosis cohort for outcomes of the Fatigue Assessment Scale (FAS), the cough, urge to cough and the Fatigue Visual Analogue Scales (VAS).

### 4.5.3 Exploratory Endpoints

The home FVC (ml) absolute decline >10% compared to baseline occurring at least in 3 consecutive days will be presented by study periods. The number of patients with and without a decline and the number of occurrences of a categorical decline will be summarized in each diagnosis cohort. The overall duration of all observed categorical declines per patient (days) will be summarized descriptively.

With respect to the evaluation of the collaboration platform by means of a survey among investigators and the digital solution set up by means of a patient questionnaire, descriptive frequency tables will be prepared at the end of the trial. Please refer to Appendix 6 for further information about the patient survey.

### 4.5.4 Sensitivity Analyses

The following sensitivity analyses related to be primary endpoint will be presented:

- The time-adjusted semi-annual mean FVC decline (mL) during peri-diagnostis period estimated from good blow quality daily home spirometry measurements excluding measurements with a difference >50% or <50% from baseline site FVC.

- The time-adjusted semi-annual mean FVC decline (mL) during peri-diagnostis period estimated from good blow quality daily home spirometry measurements excluding patients with measurements collected for less than 30 days after baseline.

- The two analyses specified above will be repeated to estimate the semi-annual mean FVC decline during the peri-diagnosis period by a single arm repeated measures mixed model with patient effects and day of measurement fitted as random effects.

In addition, sensitivity analyses to the primary analysis may be performed using a repeated measures mixed model by including additional factors and covariates (e.g. gender, height) into the model.

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

### 4.5.5 Subgroup Analyses

The different subgroups that will be used for subgroup analyses are described in detail within Section 4.4.3.3

The primary endpoint will be repeated for all agreed subgroups in Section 4.4.3.3, as well as linear regression analysis using site spirometry data.

ILD/IPF diagnosis summary table, time from enrollment to diagnosis and time to treatment start (from enrollment and from diagnosis) will be reproduced by community/tertiary sites subgroup. Moreover, time from enrollment to diagnosis will be also presented by patients having/not having lung biopsy.

In addition, disease relevant optional assessments summary table will be created by community/tertiary sites subgroup and by country.

In an additional analysis it will be investigated if a FVC decline after three months can predict the annual decline in FVC for individual patients. In the publication from Russell et al. (2016) it is stated that “three-month rate of change predicts disease progression at 1 year”. This analysis will be performed for patients diagnosed with IPF or non-IPF ILD having a minimum of 1 year of observation time, i.e. patients with daily measurements collected for at least 1 year after baseline. The estimated 3 monthly decline and annual decline will be plotted and a Pearson’s correlation coefficient will be calculated. This analysis will be presented in the final analysis of the study.

For progressing and non-progressing patients, patients requiring respiratory-related hospitalizations and the different ILD subgroups, baseline characteristic tables (demographics, medical history, time to first IPF/ILD diagnosis and duration of pre- and post-diagnosis periods) will be repeated for the final analysis.

## 4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

## 4.7 SAFETY ANALYSES

### 4.7.1 Safety Endpoints

The following safety endpoints will be analyzed descriptively by diagnosis cohorts:

- **Non-elective hospitalization, both respiratory and all cause:** a listing and a frequency table will be provided displaying number of patients with at least one non-elective hospitalization, the number of non-elective hospitalizations, the number of patients with at least one respiratory-related non-elective

hospitalization and the number of respiratory-related non-elective hospitalizations during pre- or post-diagnosis periods by diagnosis cohorts.

- **Investigator-reported acute exacerbations:** a listing and a frequency table will be provided displaying number of patients with at least one acute exacerbation and number of acute exacerbations during pre- and post-diagnosis periods by diagnosis cohorts. Additionally, number of patients and events will be given separately for triggered and idiopathic acute exacerbations. Acute exacerbation are defined as per Collard et al. 2016: answering No to the eCRF question "Is there an extra-parenchymal cause identified?"; and answering Yes to the eCRF question "Are there new, bilateral GGO (Ground glass opacification)/ consolidation on CT?" Please refer to Appendix 8 for further information.
- **Death, all cause and respiratory-related:** a listing and a frequency table is given including number of deaths during pre- and post-diagnosis period, primary cause of death and frequencies with respect to autopsies performed.

- **Events related to the study assessments:** documented events will be coded with MedDRA version 21.1 or a higher one. Frequencies of events will be displayed by System Organ Class (SOC) and Preferred Terms (PT) by diagnosis cohorts. In addition, summary of the events characteristics, events by intensity and leading to study discontinuation will be presented separately. The tables will be provided for events occurring during the peri-diagnosis period. If the start date of an event is after or on the day of the enrollment visit or it is ongoing at enrollment visit and the end date of the event is after the day of the initial diagnosis visit, the event belongs to the peri-diagnosis period. A listing with all events will be also presented.

If for any of the above mentioned events an incidence rate of more than 15% is observed, time to event analyses according to the method of Kaplan-Meier will additionally be provided.

### 4.7.2 Vital Signs

A summary table displaying vital signs values (heart rate, systolic and diastolic blood pressure) by visit and changes from baseline will be provided by diagnosis cohorts. In case more than one visit was performed during the pre- and post-diagnosis period, mean parameter values of these visits will be used for the derivation of descriptive statistics.

### 4.7.3 Previous and Concomitant Medication

Previous and concomitant medications will be coded using the Genentech (GNE) drug dictionary. This is a proprietary Roche Dictionary which is used to code concomitant

medications in the Trial Management System (TMS) coding tool. The Standardized Medication Name (CMDECOD), which is the medication generic or combination generic as defined by the Drug Thesaurus (proprietary Genentech/Roche dictionary), and the Medication Class (CMCLAS), which is the primary medication class as defined by the Drug Thersaurus, will be used for the analyses

Medications will be classified as previous, concomitant or post as follows:

Previous: If the medication end date is prior to the day of the enrollment visit.

Concomitant: If medication start date is on or after the day of the enrollment visit or if the medication start date is prior to the day of the enrollment visit but ongoing at the day of the enrollment visit, i.e. is taken during the peri-diagnosis period.

Post: if the medications start date occurred after the diagnosis date, i.e. the medication started in post-diagnosis period.

The number and frequencies of patients taking previous, concomitant and post medications will be presented by Medication Class and Standardized Medication Name. If patients receive more than one drug within a Medication Class or Standardized Medication Name they will be counted only once for the respective Medication Class or Standardized Medication Name.

## 4.8 MISSING DATA

In general, missing data will not be imputed. Exceptions will be made for events related to study assessments and concomitant medications. Here, missing start or end dates will only be imputed for the determination of whether the event or medication is allocated to the pre-, post- or peri-diagnosis period or whether the medication is considered as previous, concomitant or post medication as defined in section 4.7.3.

For events related to study assessments it is not expected that in case of partially missing dates only the year is given. In case the start/end day of the event is missing it will be imputed with the first/last day of the respective month assuring that the start/end date is after the day of the enrollment visit. In case the date is completely missing, it will be assumed that the event occurred during peri-diagnosis period.

If the medication start date is partially missing the day and month will be imputed with the earliest possible date but not prior to the date of enrollment. If the medication end date is partially missing the day and month will be imputed with the latest possible date not after death or end of study (i.e. DEC for month and 28/29/30/31 for day). In case the start/end date of a medication is completely missing, it will not be imputed and the medication will be considered a concomitant medication.

## 4.9 INTERIM ANALYSES

Interim analysis was performed in December 2018 with a cutoff date 5. October 2018. The first interim analysis (IA) was planned when 20 patients enrolled are diagnosed with IPF and can be fully evaluated with regard to the pre-diagnosis period. Finally, 25 IPF diagnosed patients were included in the first IA.

After first IA in December 2018 and a review of the data at a SC meeting in January 2019 together with completion of enrollment in February 2019 it was decided to repeat the first interim analysis during 2019 for publication at European Respiratory Society (ERS) in 2019.

## 5. REFERENCES


American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277–304.

Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199–203.

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.

Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005;353:2229–42.

Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: Impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med 2000;161:1172–8.

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Gribbin J, Hubbard RB, Le Jeune I, et al. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006;61:980–5.

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.

Hyldgaard C, Hilberg O, Muller A, et al. A cohort study of interstitial lung diseases in central Denmark. Respir Med 2014;108:793–9.

Jenkins RG, Simpson JK, Saini G, et al. Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. Lancet Respir Med 2015;3:462–72.

Mapel DW, Hunt WC, Utton R, et al. Idiopathic pulmonary fibrosis: survival in population based and hospital based cohorts. Thorax 1998;53:469–76.

Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007;176:277–84.

Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax 2012;67:804–10.

Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004;350:125–33.

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.

Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015;192:e3-19.

Raghu G et al. Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society , Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

Russell A-M, Adamali H, Molyneaux PL, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;194:989–97.

Ryerson CJ, Collard HR. Update on the diagnosis and classification of ILD. Curr Opin Pulm Med 2013;19:453–9.

Swigris JJ, Kuschner WG, Jacobs SS, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax 2005;60:588–94.

Wapenaar-deKorver M, Patel A, Birring S, et al. Comparison of changes of the King's brief interstitial lung disease questionnaire (K-BILD) with other health status measures | European Respiratory Society. Eur Resp J 2016;48:PA790.

Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital

capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:830–6.

EQ-5D-5L_UserGuide_2015, EuroQol Group

Dolan P. et al.: Modeling valuations for EuroQol health states. Medical Care 1997; 35:1095-1108.

# Appendix 1
# Protocol Synopsis

| | |
|---|---|
| **TITLE:** | **AN INTERNATIONAL STUDY TO CHARACTERIZE THE DISEASE BEHAVIOUR OF IDIOPATHIC PULMONARY FIBROSIS AND INTERSTITIAL LUNG DISEASE DURING THE PERI-DIAGNOSTIC PERIOD** |
| **PROTOCOL NUMBER:** | MA39297 |
| **VERSION NUMBER:** | 1 |
| **EUDRACT NUMBER:** | 2016-005114-22 |
| **IND NUMBER:** | N/A |
| **TEST PRODUCT:** | N/A |
| **PHASE:** | N/A |
| **INDICATION:** | IDIOPATHIC PULMONARY FIBROSIS / INTERSTITIAL LUNG DISEASE |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

There is limited data available on the early course of IPF and ILD. Often clinicians require detailed information on disease behavior in order to establish a working diagnosis and to decide on further patient management. This study will characterize the disease behavior of IPF and ILD in the peri-diagnostic period. This objective will be achieved by using a multidimensional approach assessing changes in pulmonary function, measured by daily handheld spirometry, assessing physical functional capacity, measured by accelerometry, and other aspects of disease behavior (symptoms and quality of life), by using various PRO measures.

For this study, the peri-diagnostic period covers:

- the pre-diagnostic period (from inclusion into the study to diagnosis; for a maximum of 12 months).
- the post-diagnostic period (from the diagnosis to the start of drug treatment within 6 months or a maximum of 6 months after diagnosis if no treatment is started).

Specific objectives and corresponding endpoints for the study are outlined below (Table 3).

**Table 3 Objectives and corresponding endpoints**

| Objectives | Corresponding Endpoints |
|---|---|
| **Primary Objective:** | |
| • To characterize the disease behavior of IPF during the peri-diagnostic period | • Changes in pulmonary function (FVC measured in mL by daily home spirometry) |
| **Secondary Objective:** | |
| • To characterize the disease behavior of non-IPF ILD during the peri-diagnostic period | • Changes in pulmonary function (FVC measured in mL by daily home spirometry) |

| | |
|---|---|
| • To further characterize the disease behavior of IPF and non-IPF ILD in the peri-diagnostic period using a multidimensional approach | • Change in pulmonary function (FVC measured in mL and % predicted by site spirometry)<br>• Change in physical functional capacity (measured by daily home accelerometry and site 6-minute walk test [6MWT])<br>• Change in PRO measures, overall<br>  ○ Change in PRO measures during the pre-diagnosis period<br>  ○ Changes in PRO measures during the post-diagnosis period<br>• Correlation between home and site spirometry measurements of FVC<br>• Correlation between physical functional capacity assessed at home (by accelerometry) and on site (by 6MWT)<br>• Comparison of disease behavior in IPF and ILD patients<br>• Evaluate the baseline characteristics of progressing vs non-progressing patients, patients requiring respiratory-related hospitalizations<br>• Incidence of non-elective hospitalization, both respiratory and all cause<br>• Incidence of Investigator-reported acute exacerbations [a]<br>• Incidence of death, all cause and respiratory-related deaths<br>• Incidence of events related to the study assessments |
| **Exploratory objectives** | |
| • Characterization of different subgroups | • Evaluate the characteristics (baseline characteristics, changes in pulmonary function and physical activity) of different ILD subgroups, e.g. connective tissue disease associated ILD, chronic hypersensitivity pneumonitis ILD, etc., depending on available data<br>• Evaluate the characteristics (baseline characteristics, changes in pulmonary function and physical activity) of patients with no diagnosis made 12 months after inclusion into the study |
| • Evaluate the differences in FVC values at beginning of treatment, depending on reimbursement restrictions | • Differences in pulmonary function (FVC measured in mL by daily home spirometry and site spirometry) at the start of IPF drug treatment with regards to applicable local reimbursing restrictions for pirfenidone treatment in patients with IPF |
| • Evaluation of the collaboration platform | • Evaluation of the usefulness, practicality and scalability of the collaboration platform ("virtual MDT") in normal clinical practice by means of a survey among investigators at the end of the study |

| | |
|---|---|
| • Evaluation of the digital solution set up for the patients | • Evaluation of the usefulness and practicality of the digital solution provided to patients by means of a patient questionnaire (daily spirometry, accelerometry) |

6MWT=6-minute walk test; FVC=forced vital capacity; ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; MDT= multi-disciplinary team; PRO=patient-reported outcome
a) Defined by Collard and colleagues (Collard et al. 2016)

## Study Design

### Description of Study

This is an international clinical study without any investigational medicinal product that will enroll patients with a suspected diagnosis of IPF/ILD. The principal aim of the study is to characterize the disease behavior of IPF and ILD in the peri-diagnostic period, primarily based on changes in pulmonary function (according to changes in FVC measured by daily handheld spirometry performed at home and by site spirometry) and changes in physical functional capacity (measured by daily accelerometry performed at home and 6-minute walk tests [6MWT] measured on site).

A patient will be eligible for inclusion if the investigator has a suspicion that the patient may have IPF/ILD based on symptoms and radiological evidence.

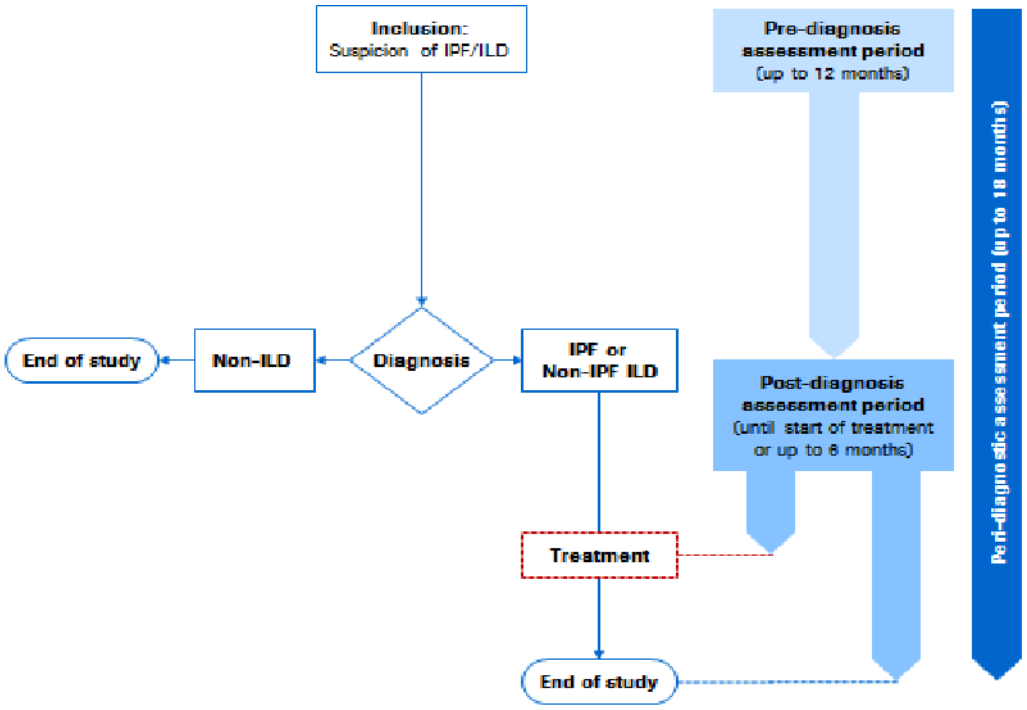
The study conduct will be facilitated by a digital ecosystem consisting of the devices used for the home-based assessments and the digital collaboration platform used to enable a “virtual” multi-disciplinary team (MDT). Patients with suspected IPF/ILD should be carefully evaluated for identifiable causes of ILD. A multidisciplinary

discussion among ILD experts is known to increase the accuracy of the diagnosis of IPF/ILD.

All patients will be managed at the discretion of the Investigator taking into account local clinical practice guidelines and standards of care as well as available clinical evidence for patients with suspected IPF/ILD or diagnosed with IPF/ILD.

The study schema is shown in Figure 1.

## Figure 1 Study Schema




ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis

From inclusion into the study, patients will be followed for a maximum of 12 months in the pre-diagnosis assessment period. Following thorough assessments and diagnoses, three groups of patients will be identified:

- Patients diagnosed with IPF.
- Patients diagnosed with an ILD other than IPF.
- Patients diagnosed with a condition that is not an ILD.

For individual patients, the end of the study will be as follows:

- Should no diagnosis be made 12 months after inclusion into the study, the patient will leave the study.
- Patients diagnosed with a non-ILD condition will leave the study on the date of diagnosis.
- Patients diagnosed with IPF or non-IPF ILD will remain and be followed in the study up to the start of drug treatment (within six months) or a maximum of six months if no drug treatment is prescribed.

“Start of drug treatment” is defined as the date when treatment commences. This includes the event of a patient receiving IPF or ILD drug treatment from a physician other than the investigator.

Accordingly, the total length of the study is variable for each patient, with a maximum of 18 months.

Site visits will be conducted at a minimum at baseline, diagnosis, and end-of-study for each individual patient. During each study period (pre- and post-diagnostic period), every patient should have at least one site visit, scheduled at the discretion of the Investigator. During these visits, any relevant information such as treatments given and results from HRCTs, radiographs, $_{DLCO,}$ lung biopsies etc. will be collected, as available.

The 6MWT and FVC measurements will be assessed on-site as per the Schedule of Activities (Appendix 1).

The study will be conducted under the leadership of a Steering Committee.

In the absence of the use of any therapeutic agent, an Independent Review Committee IRC/IRF or a Data Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMC) will not be needed in this study.

**Patient study-specific assessments / study kit**

Upon study enrollment, each patient will receive a study kit with a unique identifier containing the following:

- Hand-held spirometer (Device to measure daily FVC at home).
- Accelerometer (Device to continuously measure daily activities, such as steps per day, physical activity level).
- A tablet computer for the visualization of the spirometry and accelerometry data and conduit for data transmission to the collaboration platform; the tablet will be pre-configured to only allow use for the purpose of the study.
- A user manual for the above mentioned devices.

In addition PRO measures will be assessed. Patients will complete specific questionnaires (the King's Brief Interstitial Lung Disease [K-BILD], modified Medical Research Council [mMRC], EuroQoL Five-Dimension 5-level version [EQ-5D-5L], and Fatigue Assessment Scale [FAS] questionnaires), and visual analogue scales (VAS) for cough, urge to cough, and fatigue at inclusion in the study and afterwards just prior or during visits, upon request from the Investigator.

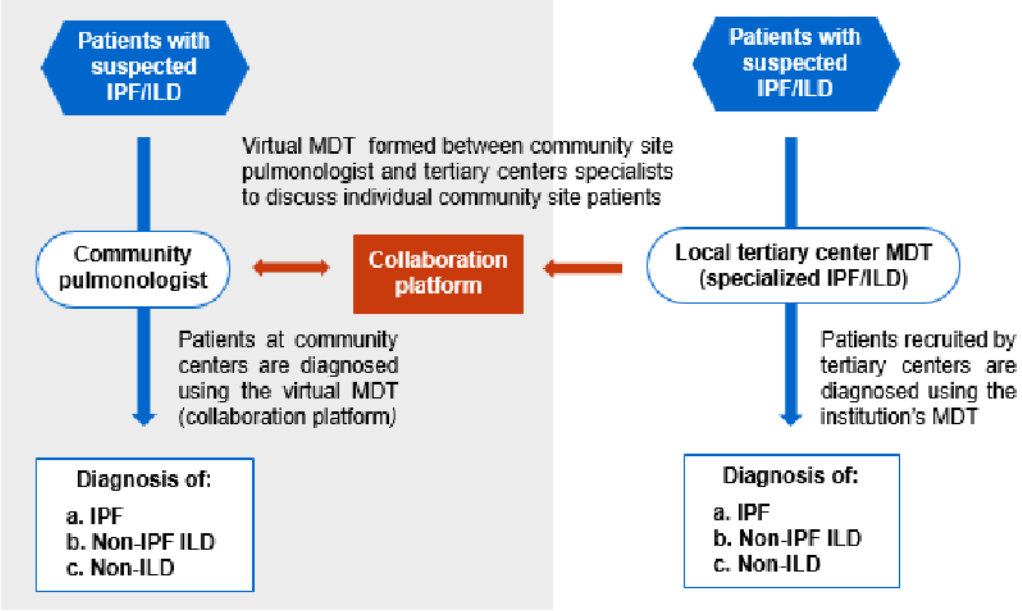
**Investigators and collaboration platform / digital eco-system**

Investigators will be located at tertiary referral centers (IPF/ILD centers) as well as smaller community sites.
The study will provide a digital collaboration platform (Figure 2) allowing investigators from community centers to interact with experts from tertiary centers (pulmonologists, radiologists, pathologists etc.), thus creating a "virtual" MDT. The investigators from community center will be able to upload any results of diagnosis-relevant assessments such as radiographs, HRCT images. This virtual MDT will then be able to discuss each patient's case. This platform is for the exclusive use of the investigators; the study sponsor will not have access to it.

The use of the platform as a means of collaboration is not mandatory for participating sites. However, investigators will access the data from daily spirometry and accelerometry of their patients on the platform. Patient data will only be accessible by

the treating physician (investigator) who can then decide to share them with the virtual MDT. These patient data will also be transferred in an anonymized way to the study database on a daily basis.

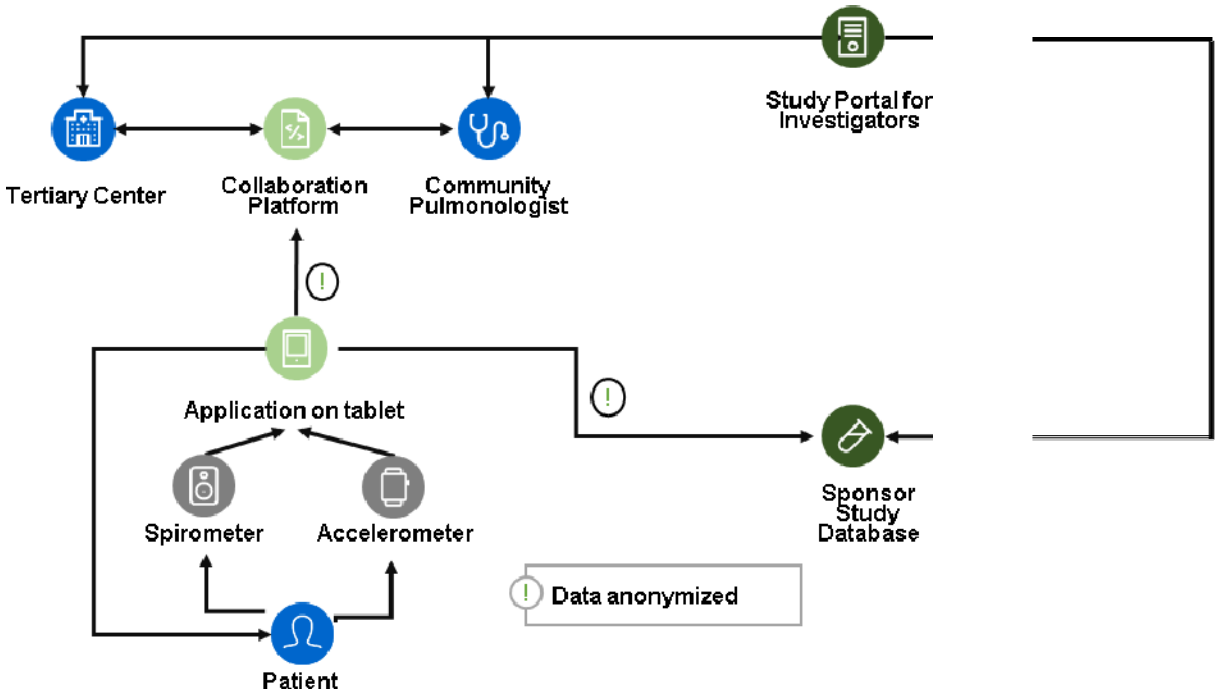
**Figure 2 Collaboration Platform**




ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; MDT=multi-disciplinary team

Figure 3 shows the overall study digital ecosystem.

**Figure 3 Study Digital Ecosystem**




**Number of Patients**

Approximately 180 patients will be enrolled at about 50 study centers in seven countries (Canada, Russia and Europe).

It is assumed that approximately 40% of the patients will be diagnosed with IPF and the remaining 60% of patients will either be diagnosed with a non-IPF ILD (approximately 50%) or with a disease other than ILD or no diagnosis (approximately 10%, i.e. approx. 18 patients). Thus, approximately 72 patients with IPF and 90 patients with non-IPF ILD are anticipated to have data available for the evaluation of the primary and secondary objectives of the study.

Patients leaving the study prematurely will not be replaced.

At least one tertiary center will be included in every participating country.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Able to comply with the study protocol, in the investigator's judgment – for example, the ability to use the provided spirometer and tablet and the ability to fill in the required patient reported outcomes questionnaires
3. Age ≥50 years

4. Suspicion of IPF/ILD: Radiological evidence of IPF/ILD in symptomatic patients (unexplained dyspnea on exertion and/or cough)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry: 1.

Participation in any investigational study within 28 days prior to inclusion

2. History of clinically significant cardiac disease that could explain the patient's symptomatology in the opinion of the investigator
3. Known history of any connective tissue disease, including, but not limited to, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, or mixed connective tissue disease.

**End of Study**

The end of the clinical study is defined as the date at which the last data point which is required for the statistical analysis is received.

**Length of Study**

The first patient is expected to enroll in Q3 of 2017, and enrollment is anticipated to continue for approximately 12 months. The last patient will complete the clinical study in early 2020 at the latest. For each patient, the total length of the study is variable (up to 18 months) and depends on local clinical practice.

**Investigational Medicinal Products**

There is no investigational drug involved in the study.

**Statistical Methods**

**Primary Analysis**

The main purpose of this study is hypothesis generation regarding the impact on pulmonary function in terms of the change in FVC, as measured by daily handheld spirometry, in patients suspected to suffer from IPF.

The primary endpoint of the study is the time-adjusted semi-annual FVC decline (in mL) in patients with IPF during the peri-diagnostic period.

For the cohort under observation (i.e. patients diagnosed with IFP), the estimated time-adjusted FVC decline (mL) will be presented descriptively, along with the corresponding two-sided 95% confidence interval.

The statistical analysis of the primary endpoint will be performed by calculating the mean FVC decline in the corresponding study cohort (i.e., patients diagnosed with IPF). The mean FVC declines will be calculated using the estimated FVC decline for each individual patient. The individual FVC decline will be estimated by applying a linear regression model to all data points collected during the study period.

The mean FVC decline (mL) will also be provided for pre-specified time periods at 3, 6 or 12 months, together with corresponding 95% confidence intervals.

**Determination of Sample Size**

For this study, a total sample size of approximately 180 patients is planned. The majority of the patients will be enrolled into two study cohorts, i.e., patients with a diagnosis of IPF or

non-IPF ILD. Due to the uncertainty of the numbers of patients to be enrolled into these two cohorts, the sample size cannot be derived for a certain patient number. For the purpose of sample size and power calculation, it is assumed that approximately 40% of patients will be diagnosed with IPF and 50% of patients will be diagnosed with non-IPF ILD. Approximately 10% of patients are expected to suffer from a disease other than ILD (non-ILD) or will not have a diagnosis within 12 months of enrollment. This assumption is based on published data (Wapenaar-deKorver et al. 2016).

Thus, it is expected to enroll approx. 72 patients with a diagnosis of IPF and approx. 90 patients with a diagnosis of non-IPF ILD.

### Table 4 Sample Size Scenarios

| Number of patients with IPF | Mean FVC decline [mL] over 6 months | Lower Bound of 95% CI | Upper Bound of 95% CI | Total number of patients to be enrolled |
|---|---|---|---|---|
| 72 | 25 | 8.83 | 41.17 | 180 |
| 72 | 50 | 33.83 | 66.17 | 180 |
| 72 | 75 | 58.83 | 91.17 | 180 |

CI = confidence interval

In Table 2 point estimates and 95% confidence intervals based on a normal distribution are tabulated for a range of possible outcomes, assuming 72 patients analyzed, a standard deviation of 70 ml, and a precision of 16.17% (estimates produced using nQuery, version 7). A mean semi-annual FVC decline in the IPF group of 50 mL is considered being a clinically relevant decline and a reasonable expectation in accordance with the literature (Ley et al. 2011). In addition, after inspection of historical data, it can be assumed that the common standard deviation in mean FVC decline is 70 mL as measured by handheld spirometry.

**Interim Analyses**

Interim analyses will be performed at least once per year. The first interim analysis is planned when 20 patients enrolled are diagnosed with IPF and can be fully evaluated with regard to the pre-diagnostic period.

[redacted]

[redacted]

## Appendix 2
## Schedule of Assessments

| | Enrollment (Suspicion of IPF/ILD) [Baseline visit] | Pre-diagnosis Assessment period (max 12 months) [a] [Visit 1] | Day of initial Diagnosis [Visit 2] | Post-diagnosis Assessment period (max. 6 months) [a] [Visit 3] | End of study / Early termination [b] [End of Study visit] |
|---|---|---|---|---|---|
| Informed consent [c] | x | | | | |
| Review of inclusion/exclusion criteria | x | | | | |
| Demographic data | x | | | | |
| General medical history and baseline conditions | x | | | | |
| **Physical examination:** | | | | | |
| Vital signs and weight | x | x | x | x | x |
| Height and body mass index (BMI) | x | | | | |
| Disease-relevant data, as available [d] | x | x | x | x | x |
| **Home-based assessments:** | | | | | |
| Daily spirometry [e] | x | x | x | x | x |
| Daily physical functional capacity assessments [f] | x | x | x | x | x |
| PRO [g] | x | x | x | x | x |
| **Site assessments:** | | | | | |
| FVC | x | x | x | x | x |
| 6MWT [h] | x | x | x | x | x |
| Serum sample for biomarker assessment **(optional)** [i] | x | | | | |
| Whole blood sample for biomarker assessment **(optional)** [i] | x | | | | |
| Concomitant medications [j] | x | x | x | x | x |

| | Enrollment (Suspicion of IPF/ILD) [Baseline visit] | Pre-diagnosis Assessment period (max 12 months) [a] [Visit 1] | Day of initial Diagnosis [Visit 2] | Post-diagnosis Assessment period (max. 6 months) [a] [Visit 3] | End of study / Early termination [b] [End of Study visit] |
|---|---|---|---|---|---|
| Investigator / Patient survey | | | | | x |
| Non-elective hospitalizations, acute exacerbations, deaths, events related to study-assessments | | x | x | x | x |

6MWT=6-minute walk test; EQ-5D=EuroQoL Five-Dimension 5-level version; FAS=Fatigue Assessment Scale; FVC=forced vital capacity; ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; K-BILD=King's Brief Interstitial Lung Disease; mMRC=modified Medical Research Council. PRO=patient-reported outcome; VAS=Visual Analogue Scale.

[a] The length of this period may vary on an individual basis. During these assessment periods, local clinical practice should be followed; however, at least 1 site visit has to be performed.

[b] End of study for an individual patient:

- Should no diagnosis be made 12 months after inclusion into the study, the patient will leave the study.
- Patients diagnosed with a non-ILD condition will leave the study on the date of diagnosis.
- Patients diagnosed with IPF or ILD will remain and be followed in the study up to the start of drug treatment (within six months) or a maximum of six months if no drug treatment is prescribed

[c] Informed consent must be documented before any study-specific procedures are performed.

[d] Data to be collected include, but are not limited to, pulmonary function tests (e.g., FEV1, DLCO), bronchoalveolar lavage, and lung biopsy results (as available).

[e] Daily spirometry will be conducted by the patient at home using the study kit provided. Spirometry assessments (FVC) will be conducted at approximately the same time each day with the patient in a seated position.

[f] Daily physical functional capacity assessments (e.g., steps per day, calorie expenditure) will be measured on an ongoing basis using the accelerometry device provided.

[g] Patients will complete specific questionnaires (K-BILD, mMRC, EQ-5D-5L, and FAS) and visual analogue scales (cough, urge to cough, and fatigue) upon request from the Investigator.

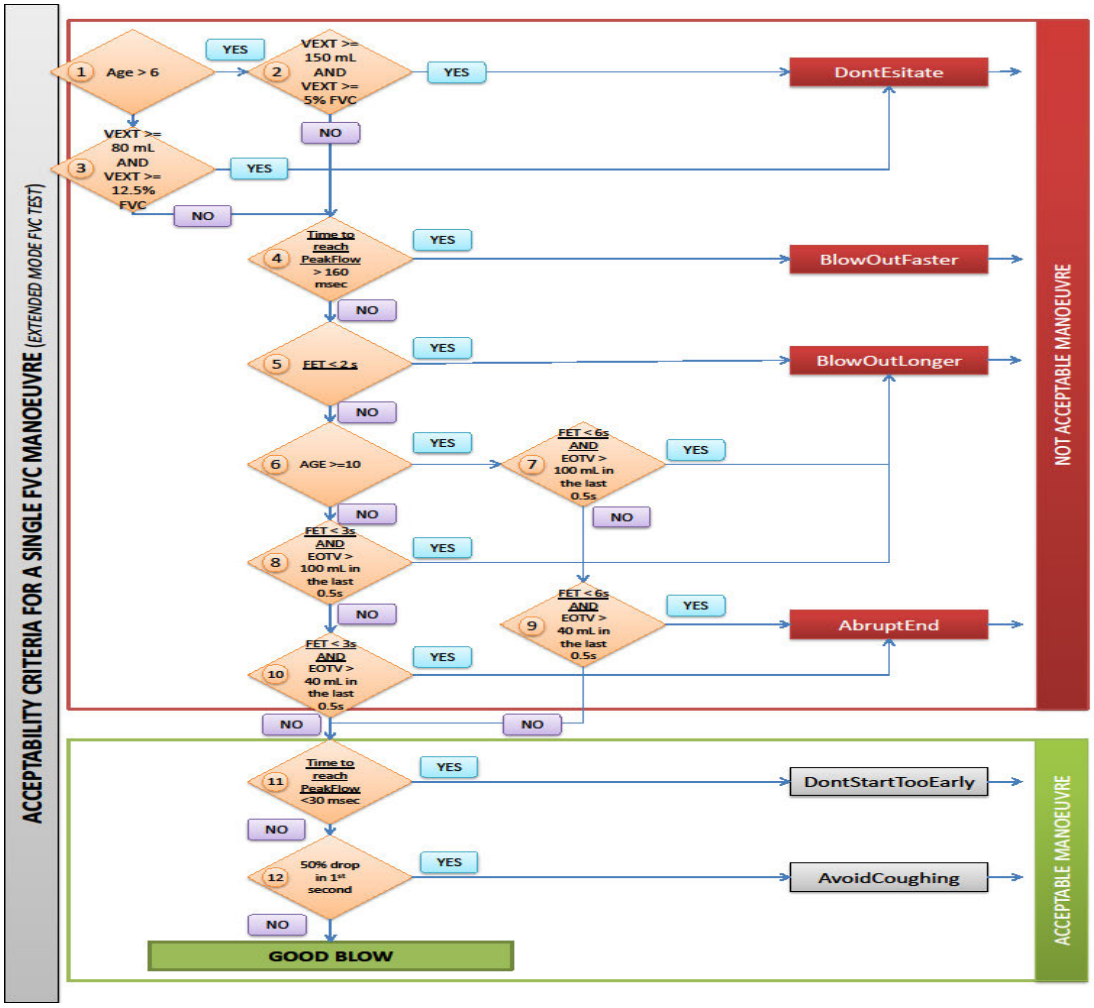
[h] The 6MWT will be performed only at sites where a formalized process is available and the test can be performed under safe conditions

[i] Providing a serum sample and a blood sample for biomarker assessment is optional for patients. Sampling will only be conducted at sites with appropriate infrastructure for blood processing.

[j] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from inclusion until the end of the study.

## Appendix 3
## Acceptability criteria for a single FVC manoeuvre

VEXT = Extrapolated Volume; FET = Forced Expiratory Time; EOTV = Volume at the End of Test (Volume time plateau)



## Appendix 4
## Patient-reported Outcome Questionnaires

### King's Brief Interstitial Lung Disease (K-BILD) Questionnaire

For derivation of K-BILD scores no documentation is available. The calculation of scores is implemented in an Excel sheet. Details will be described below.

**Table 5 K-BILD Questions**

| Question no. | code | Question |
|---|---|---|
| 1 | KBILD1 | In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill. |
| 2 | KBILD2 | In the last 2 weeks, because of my lung condition, my chest has felt tight. |
| 3 | KBILD3 | In the last 2 weeks have you worried about the seriousness of your lung complaint? |
| 4 | KBILD4 | In the last 2 weeks have you avoided doing things that make you breathless? |
| 5 | KBILD5 | In the last 2 weeks have you felt in control of your lung condition? |
| 6 | KBILD6 | In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps? |
| 7 | KBILD7 | In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'. |
| 8 | KBILD8 | In the last 2 weeks, my lung condition has made me feel anxious. |
| 9 | KBILD9 | In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest? |
| 10 | KBILD10 | In the last two weeks how much of the time have you felt your lung disease is getting worse? |
| 11 | KBILD11 | In the last 2 weeks has your lung condition interfered with your job or other daily tasks? |
| 12 | KBILD12 | In the last 2 weeks have you expected your lung complaint to get worse? |
| 13 | KBILD13 | In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries? |
| 14 | KBILD14 | In the last 2 weeks, has your lung condition made you think more about the end of your life? |
| 15 | KBILD15 | Are you financially worse off because of your lung condition? |

For each question one out of seven possible answers can be selected, coded 1 to 7.

The K-BILD questionnaire provides a total score and three subscores. The scores will be calculated on basis of the following individual items:

- Psychological: Q3, Q5, Q6, Q8, Q10, Q12, Q14
- Breathlessness and activities: Q1, Q4, Q11, Q13
- Chest symptoms: Q2, Q7, Q9

- Total score: all individual items, Q1 to Q15

For missing items the average scores of the non-missing items of this score will be imputed. Scores will only be calculated when missing data <50% per domain, else the score will be set to 'missing'.

Answers will be recoded according to the following matrix:

**Table 6 K-BILD Recode Matrix**

| 6. | Answers | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Question no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| 1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 2 | 0 | 0 | 1 | 1 | 2 | 2 | 3 | |
| 3 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 4 | 0 | 0 | 1 | 1 | 2 | 2 | 3 | |
| 5 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | |
| 6 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | Recode values |
| 7 | 0 | 0 | 1 | 1 | 2 | 2 | 3 | |
| 8 | 0 | 0 | 1 | 1 | 2 | 2 | 3 | |
| 9 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | |
| 10 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 11 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 12 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 13 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | |
| 14 | 0 | 1 | 2 | 3 | 4 | 4 | 5 | |
| 15 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | |

Scores will be derived by summing recoded values and selecting the associated logit scores as described below. Logit scores cover a range of 0 to 100.

**Table 7 K-BILD Logits**

| Psychol | Logit | | B&A | Logit | | Chest | Logit | | Total | Logit |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 |
| 1 | 10,6 | | 1 | 10,4 | | 1 | 17,3 | | 1 | 9,2 |
| 2 | 17,5 | | 2 | 17,7 | | 2 | 32,1 | | 2 | 15,3 |
| 3 | 21,9 | | 3 | 22,9 | | 3 | 44 | | 3 | 19,4 |
| 4 | 25,3 | | 4 | 27 | | 4 | 54,3 | | 4 | 22,6 |
| 5 | 28 | | 5 | 30,3 | | 5 | 63,7 | | 5 | 25,1 |
| 6 | 30,2 | | 6 | 33,1 | | 6 | 73,4 | | 6 | 27,2 |
| 7 | 32,2 | | 7 | 35,6 | | 7 | 85,2 | | 7 | 29 |
| 8 | 33,9 | | 8 | 37,8 | | 8 | 100 | | 8 | 30,5 |
| 9 | 35,5 | | 9 | 39,9 | | | | | 9 | 32 |
| 10 | 37 | | 10 | 41,9 | | | | | 10 | 33,3 |
| 11 | 38,5 | | 11 | 43,9 | | | | | 11 | 34,4 |
| 12 | 39,8 | | 12 | 45,9 | | | | | 12 | 35,5 |
| 13 | 41,2 | | 13 | 48 | | | | | 13 | 36,5 |

| Psychol | Logit | | B&A | Logit | | Chest | Logit | | Total | Logit |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 42,5 | | 14 | 50,2 | | | | | 14 | 37,5 |
| 15 | 43,8 | | 15 | 52,5 | | | | | 15 | 38,4 |
| 16 | 45,1 | | 16 | 55,2 | | | | | 16 | 39,3 |
| 17 | 46,4 | | 17 | 58,5 | | | | | 17 | 40,1 |
| 18 | 47,7 | | 18 | 62,7 | | | | | 18 | 40,9 |
| 19 | 49,1 | | 19 | 68,8 | | | | | 19 | 41,7 |
| 20 | 50,5 | | 20 | 79,9 | | | | | 20 | 42,4 |
| 21 | 52 | | 21 | 100 | | | | | 21 | 43,2 |
| 22 | 53,5 | | | | | | | | 22 | 43,9 |
| 23 | 55,2 | | | | | | | | 23 | 44,6 |
| 24 | 56,9 | | | | | | | | 24 | 45,2 |
| 25 | 58,8 | | | | | | | | 25 | 45,9 |
| 26 | 60,8 | | | | | | | | 26 | 46,5 |
| 27 | 63 | | | | | | | | 27 | 47,2 |
| 28 | 65,5 | | | | | | | | 28 | 47,8 |
| 29 | 68,3 | | | | | | | | 29 | 48,5 |
| 30 | 71,6 | | | | | | | | 30 | 49,1 |
| 31 | 75,6 | | | | | | | | 31 | 49,7 |
| 32 | 80,9 | | | | | | | | 32 | 50,4 |
| 33 | 88,6 | | | | | | | | 33 | 51 |
| 34 | 100 | | | | | | | | 34 | 51,6 |
| | | | | | | | | | 35 | 52,2 |
| | | | | | | | | | 36 | 52,9 |
| | | | | | | | | | 37 | 53,5 |
| | | | | | | | | | 38 | 54,1 |
| | | | | | | | | | 39 | 54,8 |
| | | | | | | | | | 40 | 55,4 |
| | | | | | | | | | 41 | 56,1 |
| | | | | | | | | | 42 | 56,7 |
| | | | | | | | | | 43 | 57,4 |
| | | | | | | | | | 44 | 58,1 |
| | | | | | | | | | 45 | 58,8 |
| | | | | | | | | | 46 | 59,5 |
| | | | | | | | | | 47 | 60,2 |
| | | | | | | | | | 48 | 61 |
| | | | | | | | | | 49 | 61,8 |
| | | | | | | | | | 50 | 62,6 |
| | | | | | | | | | 51 | 63,5 |
| | | | | | | | | | 52 | 64,4 |
| | | | | | | | | | 53 | 65,3 |
| | | | | | | | | | 54 | 66,4 |
| | | | | | | | | | 55 | 67,5 |
| | | | | | | | | | 56 | 68,7 |
| | | | | | | | | | 57 | 70 |
| | | | | | | | | | 58 | 71,5 |
| | | | | | | | | | 59 | 73,2 |
| | | | | | | | | | 60 | 75,2 |
| | | | | | | | | | 61 | 77,6 |
| | | | | | | | | | 62 | 80,6 |
| | | | | | | | | | 63 | 84,6 |
| | | | | | | | | | 64 | 90,8 |
| | | | | | | | | | 65 | 100 |

## Appendix 5
## Community and tertiary sites

| Site Country | Site # | Tertiary (T) or Community (C) site? |
|---|---|---|
| CANADA | [redacted] | C |
| CANADA | | C |
| CANADA | | C |
| CANADA | | T |
| FRANCE | | T |
| FRANCE | | T |
| FRANCE | | T |
| FRANCE | | T |
| FRANCE | | T |
| FRANCE | | C |
| FRANCE | | T |
| FRANCE | | C |
| FRANCE | | C |
| FRANCE | | C |
| FRANCE | | C |
| IRELAND | | T |
| IRELAND | | C |
| ITALY | | C |
| ITALY | | C |
| ITALY | | T |
| ITALY | | C |
| ITALY | | C |
| ITALY | | T |
| ITALY | | T |
| ITALY | | C |
| ITALY | | C |
| ITALY | | C |
| ITALY | | C |
| ITALY | | C |
| NETHERLANDS | | T |
| NETHERLANDS | | C |
| NETHERLANDS | | C |

| | | |
|---|---|---|
| RUSSIAN FEDERATION | [redacted] | C |
| RUSSIAN FEDERATION | | C |
| RUSSIAN FEDERATION | | C |
| RUSSIAN FEDERATION | | C |
| RUSSIAN FEDERATION | | C |
| RUSSIAN FEDERATION | | T |
| RUSSIAN FEDERATION | | T |

# Appendix 6
# Patient survey

**Patient survey version 1.0**

Dear Patient,
many thanks for participating in the clinical trial which you are completing now.
This trial used an intricate digital set-up to collect and report data from your spirometer and accelerometer (step counter) via the tablet you were provided with. This approach is rather new in clinical trials but we are quite certain that in the future, similar set-ups will be used.
We are very keen on learning from you how you felt about the different aspects of the set-up and thus ask you to kindly complete the questionnaire below. Your answers might also help in designing future digital trial set-ups. **THANK YOU VERY MUCH**.

1. **Was the spirometer easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

2. **Was the accelerometer (step counter) easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

3. **Was the tablet easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

4. **How easy or hard was it to incorporate the daily blow into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

5. **How easy or hard was it to incorporate the acceleromety into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

6. **How easy or hard was it to incorporate the use of the tablet into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

7. **Was the spirometer useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

8. **Was the accelerometer useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

9. **Was the tablet useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

10. **How well did you like the look and feel of the tablet views?**
    Please tick the box that applies where 1= not well done at all; 7= very well done

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

11. **Did you find the reminders or notifications you received from the tablet helpful?**
    Please tick the box that applies where 1= not helpful at all; 7= very helpful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

12. **Did you find the communication with your doctor helpful (using the tablet)?**
    Please tick the box that applies where 1= not helpful at all; 7= very helpful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

13. Please tick the box that applies to each of the following statements where 1=do not agree; 7=strongly agree

    a. **Enabling my doctor to see my data helped us better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    b. **Monitoring my activity allowed me to better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    c. **Monitoring my lung function allowed me to better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    d. **In future, I would like to have the opportunity to monitor my activity.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    e. **In future, I would like to have the opportunity to monitor my lung function.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

14. **After you had your initial training on the devices, how often did you consult the user manual?**
    1=never; 2=less than 3 times; 3=more than 3 times

| 1 | 2 | 3 |
|---|---|---|

15. **How helpful was the user manual?**
    Please tick the box that applies where 1= not helpful at all; 7= very helpful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

16. **Was there any need for you to call the support helpdesk?**
    1=never; 2=less than 3 times; 3=more than 3 times

| 1 | 2 | 3 |
|---|---|---|

17. **If you did call the support helpdesk, how would you rate the support you received?**
    Please tick the box that applies where 1= not useful; 7= very useful
    Leave blank if you did not call the support helpdesk

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

**Patient survey version 2.0**

Dear Patient,

Many thanks for participating in the clinical trial which you are completing now.
This trial used an intricate digital set-up to collect and report data from your spirometer and accelerometer (step counter) via the tablet you were provided with. This approach is rather new in clinical trials but we are quite certain that in the future, similar set-ups will be used.
We are very keen on learning from you how you felt about the different aspects of the set-up and thus ask you to kindly complete the questionnaire below. Your answers might also help in designing future digital trial set-ups. **THANK YOU VERY MUCH**.

1. **Was the spirometer easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

2. **Was the accelerometer (step counter) easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

3. **Was the tablet easy to use?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

4. **How easy or hard was it to incorporate the daily blow into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

5. **How easy or hard was it to incorporate the accelerometer into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

6. **How easy or hard was it to incorporate the use of the tablet into your daily routine?**
   Please tick the box that applies where 1= very hard; 7= very easy

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

7. **Was the spirometer useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

8. **Was the accelerometer useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

9. **Was the tablet useful?**
   Please tick the box that applies where 1= not useful; 7= very useful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

10. **How well did you like the look and feel of the tablet views?**
    Please tick the box that applies where 1= not well done at all; 7= very well done

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

11. **Did you find the reminders or notifications you received from the tablet helpful?**
    Please tick the box that applies where 1= not helpful at all; 7= very helpful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

12. Please tick the box that applies to each of the following statements where 1=do not agree; 7=strongly agree

    a. **Enabling my doctor to see my data helped us better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    b. **Monitoring my activity allowed me to better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    c. **Monitoring my lung function allowed me to better manage my health.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    d. **In future, I would like to have the opportunity to monitor my activity.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

    e. **In future, I would like to have the opportunity to monitor my lung function.**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

13. **After you had your initial training on the devices, how often did you consult the user manual?**
    1=never; 2=less than 3 times; 3=more than 3 times

| 1 | 2 | 3 |
|---|---|---|

14. **How helpful was the user manual?**
    Please tick the box that applies where 1= not helpful at all; 7= very helpful

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

15. **Was there any need for you to contact your study doctor and ask for help regarding the patient kit?**
    1=never; 2=less than 3 times; 3=more than 3 times

| 1 | 2 | 3 |
|---|---|---|

# Appendix 7
# EQ-5D-5L

**Figure 1: EQ-5D-5L (UK English sample version)**

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

**MOBILITY**

| | |
|---|---|
| I have no problems in walking about | ❑ |
| I have slight problems in walking about | ❑ |
| I have moderate problems in walking about | ❑ |
| I have severe problems in walking about | ❑ |
| I am unable to walk about | ❑ |

**SELF-CARE**

| | |
|---|---|
| I have no problems washing or dressing myself | ❑ |
| I have slight problems washing or dressing myself | ❑ |
| I have moderate problems washing or dressing myself | ❑ |
| I have severe problems washing or dressing myself | ❑ |
| I am unable to wash or dress myself | ❑ |

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

| | |
|---|---|
| I have no problems doing my usual activities | ❑ |
| I have slight problems doing my usual activities | ❑ |
| I have moderate problems doing my usual activities | ❑ |
| I have severe problems doing my usual activities | ❑ |
| I am unable to do my usual activities | ❑ |

**PAIN / DISCOMFORT**

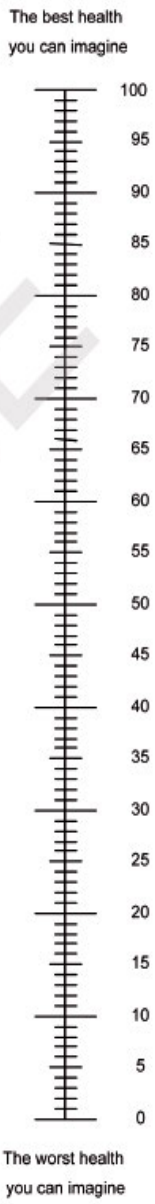
| | |
|---|---|
| I have no pain or discomfort | ❑ |
| I have slight pain or discomfort | ❑ |
| I have moderate pain or discomfort | ❑ |
| I have severe pain or discomfort | ❑ |
| I have extreme pain or discomfort | ❑ |

**ANXIETY / DEPRESSION**

| | |
|---|---|
| I am not anxious or depressed | ❑ |
| I am slightly anxious or depressed | ❑ |
| I am moderately anxious or depressed | ❑ |
| I am severely anxious or depressed | ❑ |
| I am extremely anxious or depressed | ❑ |

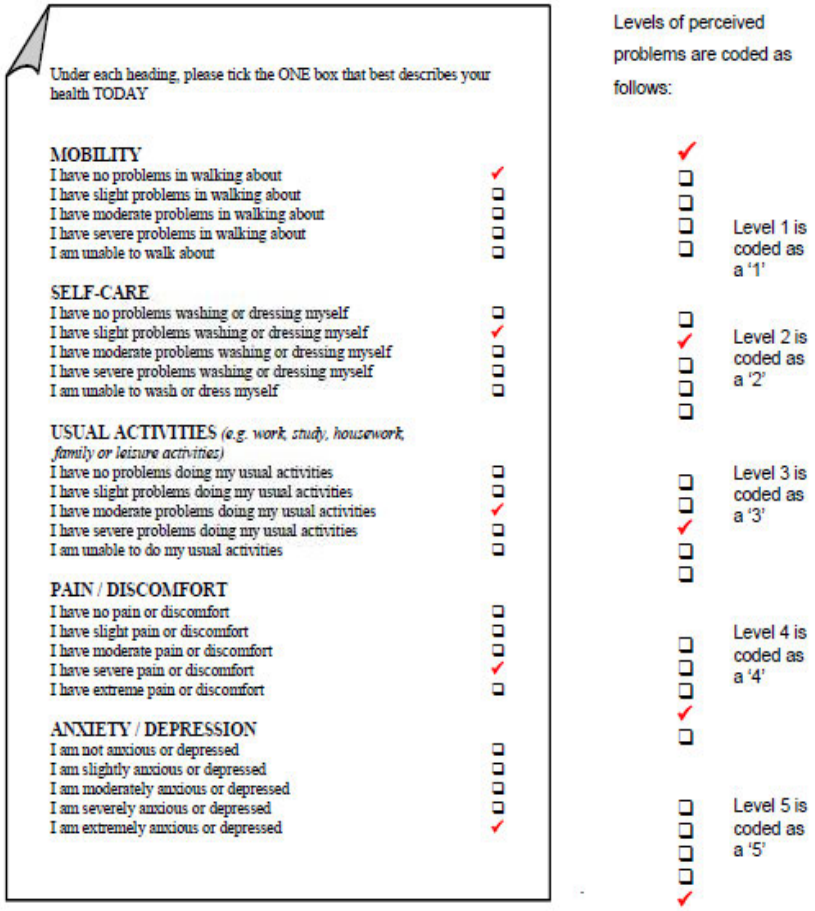
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  **0** means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

**YOUR HEALTH TODAY =** ☐



## 2. Scoring the EQ-5D-5L descriptive system

The EQ-5D-5L descriptive system should be scored, for example, as follows:



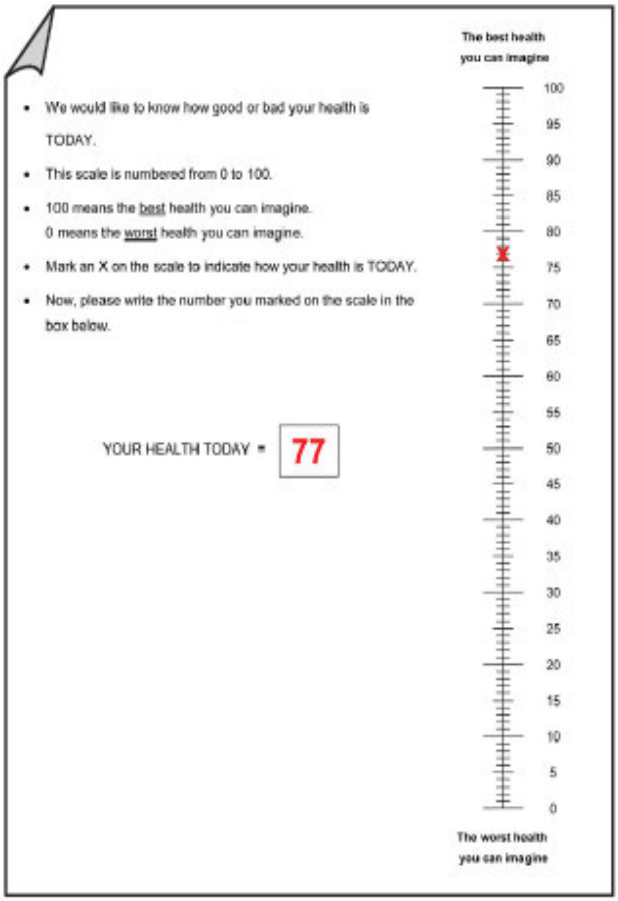

This example identifies the health state '12345'.

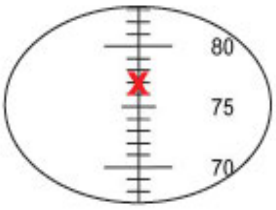
*Notes:*

- *There should be only ONE response for each dimension*
- *Missing values can be coded as '9'.*
- *Ambiguous values(e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.*

## 3. Scoring the EQ VAS

The EQ VAS should be scored, for example, as follows:




For example this response should be coded as 77

***NB: Missing values** should be coded as '999'.*

***NB:** If there is a discrepancy between where the respondent has placed the X and the number he/she has written in the box, administrators should use the number in the box.*

*Notes:*

- *Missing values should be coded as '999'.*
- *If there is a discrepancy between where the respondent has placed the X and the number he/she has written in the box, administrators should use the number in the box.*

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. Studies that directly elicit preferences from general population samples to derive value sets for the EQ-5D-5L are under development in a number of countries; however, these studies will take time to complete and for results to be disseminated.

The EuroQol Group coordinated a study4 that administered both the 3-level and 5-level versions of the EQ-5D, in order to develop a "crosswalk" between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system, resulting in crosswalk value sets for the EQ-5D-5L. A total of 3691 respondents completed both the 3L and 5L across 6 countries: Denmark, England, Italy, the Netherlands, Poland and Scotland. Different subgroups were targeted, and in most countries, a screening protocol was implemented to ensure that a broad spectrum of levels of health would be captured across the dimensions of EQ-5D for both the 5L and 3L descriptive systems. Several methods were consequently tested to optimize the link function between the two descriptive systems. The crosswalk link function resulting from this exercise can be used to calculate index values for EQ-5D-5L, based on the existing value sets for the EQ-5D-3L. Value sets have been derived for EQ-5D-3L in several countries using visual analogue scale (VAS) technique or time trade-off (TTO) valuation techniques. The list of currently available value sets with the number of respondents and valuation technique applied is presented in table 1. Most of the EQ-5D-3L value sets have been obtained using a representative sample of the general population, thereby ensuring that they represent the societal perspective. For anyone working with EQ-5D-3L data, an essential guide to the Group's available value sets can be found in: EuroQol Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide, published by Springer.

There are value sets derived for all the countries participating in this study expect for Ireland and Russia. For those, EuroQoL recommends to use the crosswalk of a country that resembles e.g. Russia most or the internationally most frequently used crosswalks (UK / USA). We will use the one from UK.

Once we do have the EQ-5D-3L derived, we could calculate the single index value in the following way, for example for UK:

**Table 4 Weights for EQ-5D-3L Single Index Utility Score Derivation**

| EuroQoL Dimension | Level 2 Weight | Level 3 Weight |
|---|---|---|
| Mobility | 0.069 | 0.314 |
| Self-care | 0.104 | 0.214 |
| Usual Activity | 0.036 | 0.094 |
| Pain/Discomfort | 0.123 | 0.386 |
| Anxiety/Depression | 0.071 | 0.236 |
| Constant* | 0.081 | 0.269 |

* The constant is applied for any level 2 or level 3 dysfunctional state (downgrading from 1 to 2 or from 2 to 3, respectively).

A health state of (1 1 1 1 1) corresponds to a single index utility score of 1, which indicates full health. The index score will not be calculated if $\geqslant$1 of the dimensions are missing.

Example:

For a health state of (1 1 2 2 3) do the following:

1. Start with a score of 1
2. Constant term for any level 2 dysfunctional state – subtract 0.081
4. Mobility level 1 – subtract 0
5. Self-care level 1 – subtract 0
6. Usual activity level 2 – subtract 0.036
7. Pain/discomfort level 2 – subtract 0.123
8. Anxiety/depression level 3 – subtract 0.236
9. Constant term for any level 3 dysfunctional state – subtract 0.269

This gives an EQ-5D single index utility score of 0.255.

# Appendix 8
# Acute exacerbations

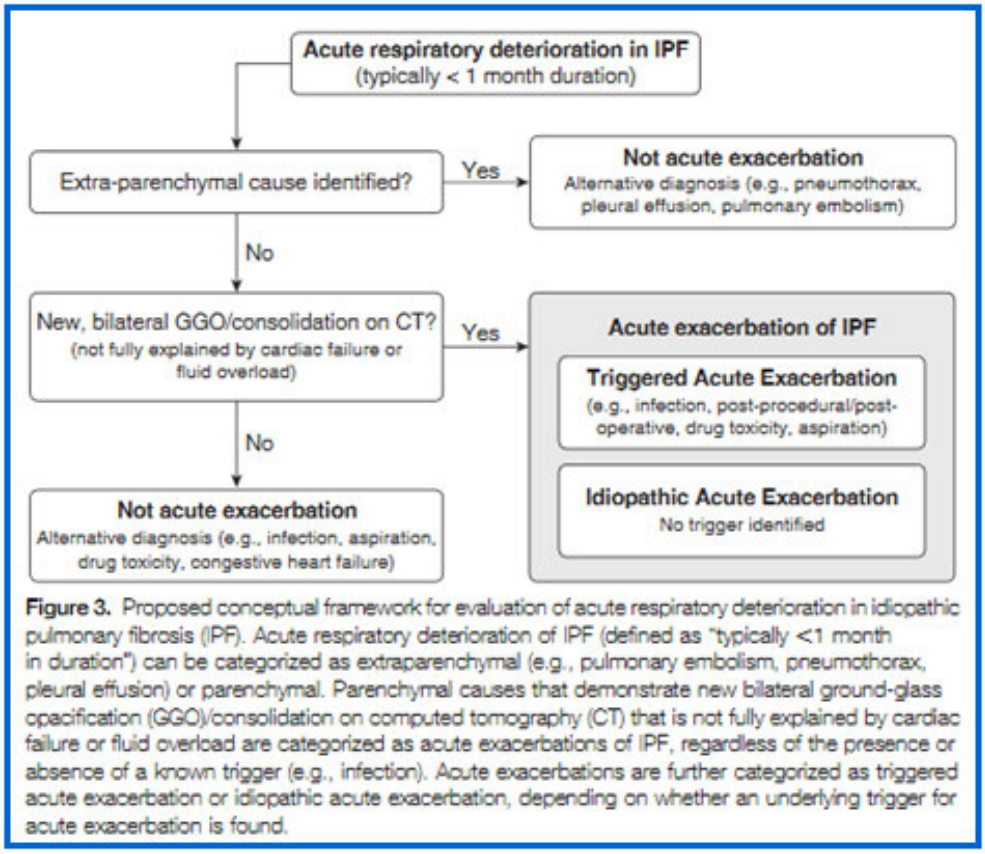



**Figure 3.** Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural 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.