

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

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PROTOCOL

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PROTOCOL ACCEPTANCE FORM

TITLE: AN INTERNATIONAL STUDY TO CHARACTERIZE THE DISEASE BEHAVIOUR OF IDIOPATHIC PULMONARY FIBROSIS AND INTERSTITIAL LUNG DISEASE DURING THE PERI-DIAGNOSTIC PERIOD

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MEDICAL MONITOR: [REDACTED]

SPONSOR: F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form {as instructed by XX [e.g., your local study monitor, the CRO]} [or] {to the contact provided below}.

{Name}

{Address}

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

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IND NUMBER: N/A

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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 1).

Table 1 Objectives and Corresponding endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
<ul style="list-style-type: none"> To characterize the disease behavior of IPF during the peri-diagnostic period 	<ul style="list-style-type: none"> Changes in pulmonary function (FVC measured in mL by daily home spirometry)
Secondary Objective:	
<ul style="list-style-type: none"> To characterize the disease behavior of non-IPF ILD during the peri-diagnostic period 	<ul style="list-style-type: none"> Changes in pulmonary function (FVC measured in mL by daily home spirometry)
<ul style="list-style-type: none"> To further characterize the disease behavior of IPF and non-IPF ILD in the peri-diagnostic period using a multidimensional approach 	<ul style="list-style-type: none"> Change in pulmonary function (FVC measured in mL and % predicted by site spirometry) Change in physical functional capacity (measured by daily home accelerometry and site 6-minute walk test [6MWT]) Change in PRO measures, overall <ul style="list-style-type: none"> Change in PRO measures during the pre-diagnosis period Changes in PRO measures during the post-diagnosis period Correlation between home and site spirometry measurements of FVC Correlation between physical functional capacity assessed at home (by accelerometry) and on site (by 6MWT) Comparison of disease behavior in IPF and ILD patients Evaluate the baseline characteristics of progressing vs non-progressing patients, patients requiring respiratory-related hospitalizations Incidence of non-elective hospitalization, both respiratory and all cause Incidence of Investigator-reported acute exacerbations ^a Incidence of death, all cause and respiratory-related deaths Incidence of events related to the study assessments

Objectives	Corresponding Endpoints
Exploratory objectives	
<ul style="list-style-type: none"> • Characterization of different subgroups 	<ul style="list-style-type: none"> • 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 • 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
<ul style="list-style-type: none"> • Evaluate the differences in FVC values at beginning of treatment, depending on reimbursement restrictions 	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Evaluation of the collaboration platform 	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Evaluation of the digital solution set up for the patients 	<ul style="list-style-type: none"> • 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.

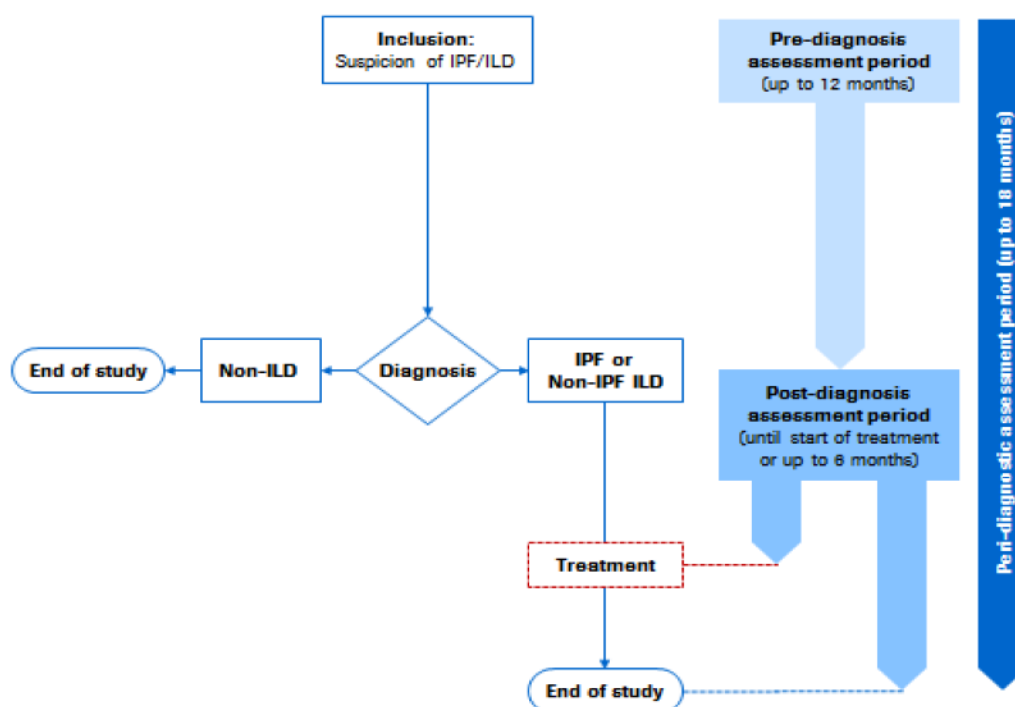
The study conduct will be facilitated by a digital ecosystem consisting of the devices used for the home-based assessments and the digital collaboration platform used to enable a "virtual" multi-disciplinary team (MDT). Patients with suspected IPF/ILD should be carefully evaluated for identifiable causes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

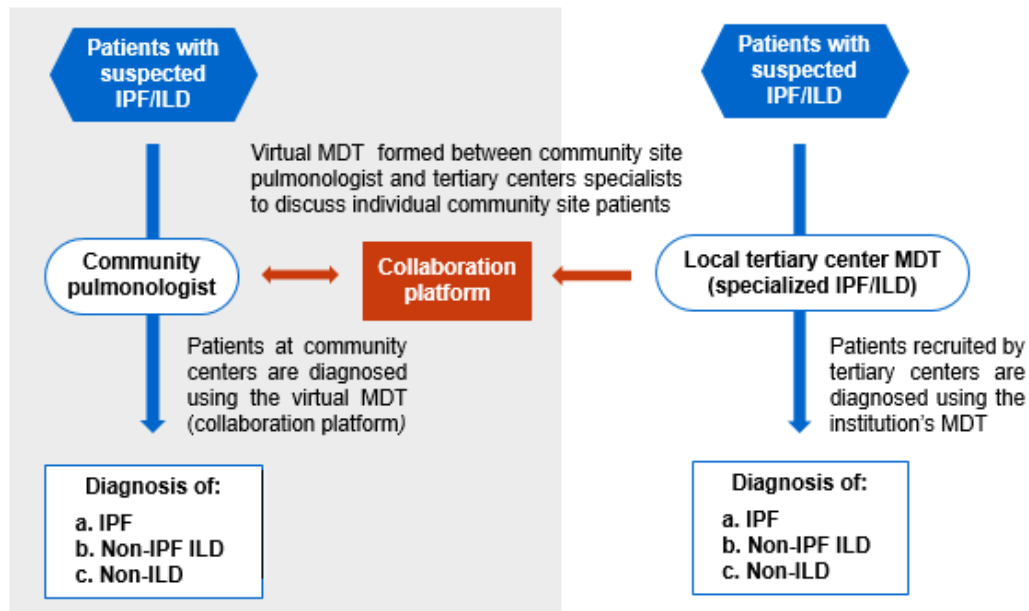
Investigators and collaboration platform / digital eco-system

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.

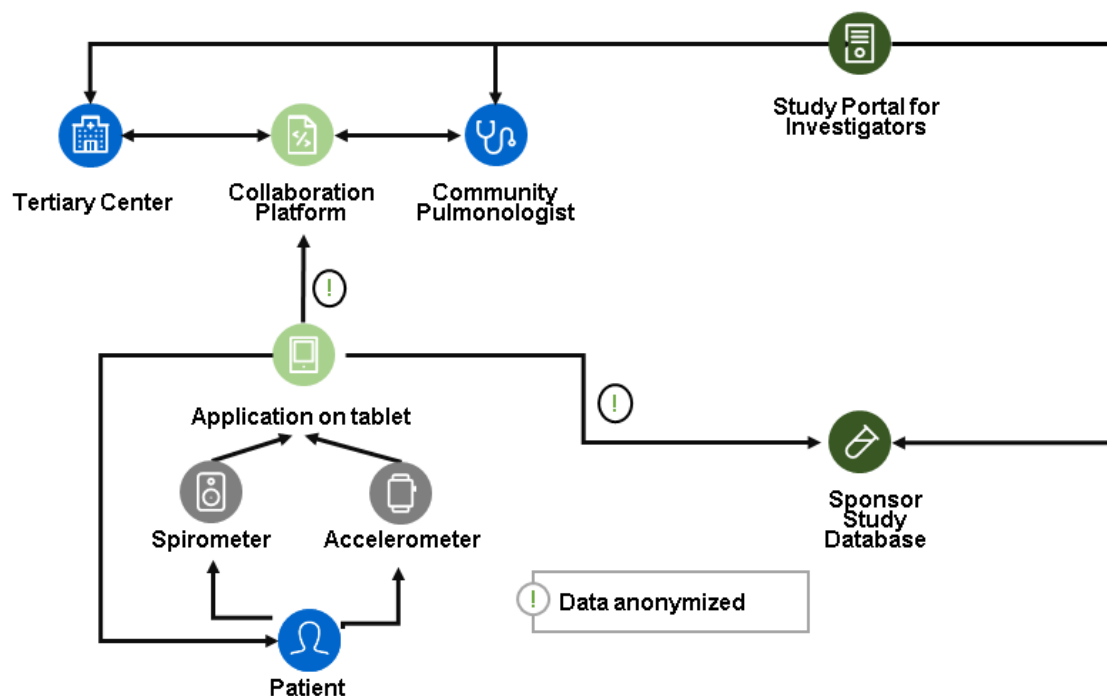
Figure 2 Collaboration Platform



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 IPF), 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 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 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]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	6-minute walk test
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BMI	body mass index
CI	confidence interval
CRO	contract research organization
DL _{CO}	carbon monoxide diffusing capacity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQoL Five-Dimension questionnaire (5-level version)
ERS	European Respiratory Society
EU	European Union
FAS	Fatigue Assessment Scale
FVC	forced vital capacity
HRCT	high-resolution computed tomography
ICH	International Council for Harmonisation
ILD	Interstitial lung disease
IMP	investigational medicinal product
IND	investigational New Drug (application)
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRC	Independent Review Committee
JRS	Japanese Respiratory Society
K-BILD	King's Brief Interstitial Lung Disease questionnaire
LPLV	last patient, last visit

MDT	multi-disciplinary team
mMRC	modified Medical Research Council questionnaire
	
NGS	next-generation sequencing
PRO	patient-reported outcome
UIP	usual interstitial pneumonia
VAS	visual analogue scale
WES	whole exome sequencing
WGS	whole genome sequencing

1 BACKGROUND

1.1 Background on Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease (IPF/ILD)

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).

Idiopathic pulmonary fibrosis is a rare disease; recent age- and gender-adjusted prevalence estimates range from 27.9 to 63.0 per 100,000 in the United States (US) by narrow and broad criteria for IPF definition, respectively. The prevalence ranged from 1.25 to 23.4 cases per 100,000 population in European Union (EU) (Fernández Pérez et al. 2010; Nalysnyk et al. 2012; Raghu et al. 2006). The observed variability in IPF prevalence may be explained by the differences in diagnostic criteria used, case definition, study population and study design. IPF is most prevalent in middle-aged and elderly patients, and most studies have found a higher frequency in men than in women (Nalysnyk et al. 2012).

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).

IPF is believed to result from a series of microinjuries to the alveolar epithelium, triggering release of profibrotic mediators. The characteristic pathologic finding on biopsy of lung tissue is a pattern of UIP with subepithelial fibroblastic foci throughout the lung.

Inflammation, although it may initially be present, is not typically a prominent histopathologic finding. Rather, an unremitting fibrotic response relocates from the alveolar space to the interstitium, with fibroblast and myofibroblast proliferation, organization into fibroblastic foci, and excessive collagen deposition and accumulation (American Thoracic Society and European Respiratory Society 2002; du Bois 2010). Although the majority of patients have a history of cigarette smoking, the etiology of IPF remains unknown.

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 is limited data available on the early course of disease in symptomatic patients with suspicion of IPF/ILD. Thus, the peri-diagnosis period (see definition section 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.

1.2 Background on Test Product

There is no investigational drug involved in the study as patients will stop the study before receiving drug treatment for IPF/ILD.

1.3 Study Rationale

The proposed study will enroll symptomatic patients with suspicion of IPF/ILD. In terms of current clinical practice, there is limited data available on the early course of disease and often clinicians require detailed information on disease behavior in order to establish a working diagnosis and to decide on further patient management.

In an era of effective anti-fibrotic therapy, early detection of disease progression should provide the opportunity to tailor therapy to an individual's disease (Russell et al. 2016). Therefore, a study to characterize the disease behavior of IPF/ILD patients during the peri-diagnostic period would provide data on the early course of disease. By following patients' lung function before and after diagnosis using home spirometry, levels of physical activity, as well as self-assessment data from the patient (patient reported outcomes; PRO), the study would provide potentially more rapid information on disease behavior and eventually progression compared to usual clinic measurements that occur only every 3-6 months.

The main goals of this study are to assess:

- the disease behavior in early IPF/ILD patients during the peri-diagnostic period
- the feasibility of handheld spirometry in a multi-center study and its potential use in daily clinical practice

Several small, generally single center clinical trials have assessed the utility of handheld spirometry and physical functional capacity evaluations in patients with IPF. Individuals with a diagnosis of IPF were recruited as a subgroup of the Prospective Observation of Fibrosis in the Lung Clinical Endpoints (PROFILE) study (Jenkins et al. 2015). One of the objectives of the study was to determine the feasibility and reliability of measuring daily FVC in individuals with IPF (See Appendix 2 – Example of Disease Behavior in an Individual Patient using home spirometry) (Russell et al. 2016). Daily measurements were recorded by 50 patients with IPF using handheld spirometers (CareFusion, United Kingdom) for a median period of 279 days. An excellent correlation was observed between handheld spirometry and hospital-obtained readings. Moreover, the rate of decline in FVC following the use of handheld spirometers was highly predictive of outcome and subsequent mortality when measured at 3, 6, and 12 months. The conclusion of the study was that daily home spirometry measurements in patients with IPF are clinically highly informative and, for the majority of patients, quite feasible to

perform. However, these observations merit to be repeated across multiple centers and countries to ensure generalizability.

Within respiratory medicine, home disease monitoring in the form of peak flow measurement is already a feature of asthma self-management and in lung transplant-recipients. Potential clinical advantages of routine home monitoring in IPF include early detection of rapidly declining FVC and monitoring of response to therapies. Home monitoring could be used to deliver personalized patient care enabling early identification and treatment of IPF related complications (Russell et al. 2016).

This study will follow patients with suspected IPF/ILD also with respect to their level of physical activity.

A German study investigated the levels of physical activity in patients with IPF and the potential associations between physical activity and lung function, exercise capacity, symptoms, and quality-of-life (Bahmer et al. 2016). Forty-eight patients with IPF were included and physical activity (steps per day, physical activity level, and minutes of moderate activity) was measured by accelerometry (SenseWear bracelet) for 1 week. The study showed that fatigue and exercise capacity were strong and independent predictors of physical activity in patients with IPF. However, this study was short and did not focus on pulmonary function assessments.

Assessments that analyze the course of IPF (disease behavior) are likely to become an important aspect of decision making in an upcoming consensus paper from the European Respiratory Society (ERS). Study MA39297 will contribute to the improvement in the rapid assessment of disease behavior.

This study will investigate course of the disease in patients with suspected IPF/ILD. By receiving data from daily home spirometry measurements, treating physicians may have an improved chance of detecting an early decline in lung function which may give supportive information in diagnostic dilemma's or guide treatment decisions.

This study also intends to foster better collaborations between IPF tertiary referral centers (IPF/ILD centers) and community center pulmonologists by creating a functional "virtual" multi-disciplinary team (MDT) which can work together for the benefit of this patient population.

In summary, the key benefits of the study will include:

- Providing data on the early course of disease as often clinicians require further information on disease behavior in order to establish a working diagnosis and to decide on further patient management.

- Allowing the patients to see their data from daily assessments and be better informed of their condition.
- Creation of “virtual” MDTs, with the aim of spreading knowledge and fostering collaboration between investigators (general pulmonologists and referral sites).

2 OBJECTIVES AND ENDPOINTS

As there is limited data available on the early course of disease and 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 using a multidimensional approach assessing changes in pulmonary function, measured by daily handheld spirometry, by assessing physical functional capacity measured by accelerometry, and by evaluation of other aspects of disease behavior (symptoms and quality of life) 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 1).

Table 1 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 characterize further the disease behavior of IPF and non-IPF ILD in the peri-diagnostic period using a multidimensional approach	<ul style="list-style-type: none"> • Change in pulmonary function (FVC measured in mL and % predicted by site spirometry) • Change in physical functional capacity (measured by daily home accelerometry and

	<ul style="list-style-type: none"> site 6-minute walk test [6MWT]) • Change in PRO measures, overall <ul style="list-style-type: none"> o Change in PRO measures during the pre-diagnosis period o Change in PRO measures during the post-diagnosis period • Correlation between home and site spirometry measurements of FVC • Correlation between physical functional capacity assessed at home (by accelerometry) and on site (by 6MWT) • Comparison of disease behavior in IPF and ILD patients • Evaluate the baseline characteristics of progressing vs non-progressing patients, patients requiring respiratory-related hospitalizations • Incidence of non-elective hospitalization, both respiratory and all cause • Incidence of Investigator-reported acute exacerbations ^a • Incidence of death, all cause and respiratory-related deaths • Incidence of events related to the study assessments
Exploratory objectives	
<ul style="list-style-type: none"> • Characterization of different subgroups 	<ul style="list-style-type: none"> • 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 • 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
<ul style="list-style-type: none"> • Evaluate the differences in FVC values at beginning of treatment, depending on reimbursement restrictions 	<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> ● Evaluation of the collaboration platform 	<ul style="list-style-type: none"> ● 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
<ul style="list-style-type: none"> ● Evaluation of the digital solution set up for the patients 	<ul style="list-style-type: none"> ● Evaluation of the usefulness and practicality of the digital solution provided to the 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)

3 STUDY DESIGN

3.1 Description of the Study

This is an international clinical study, without 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).

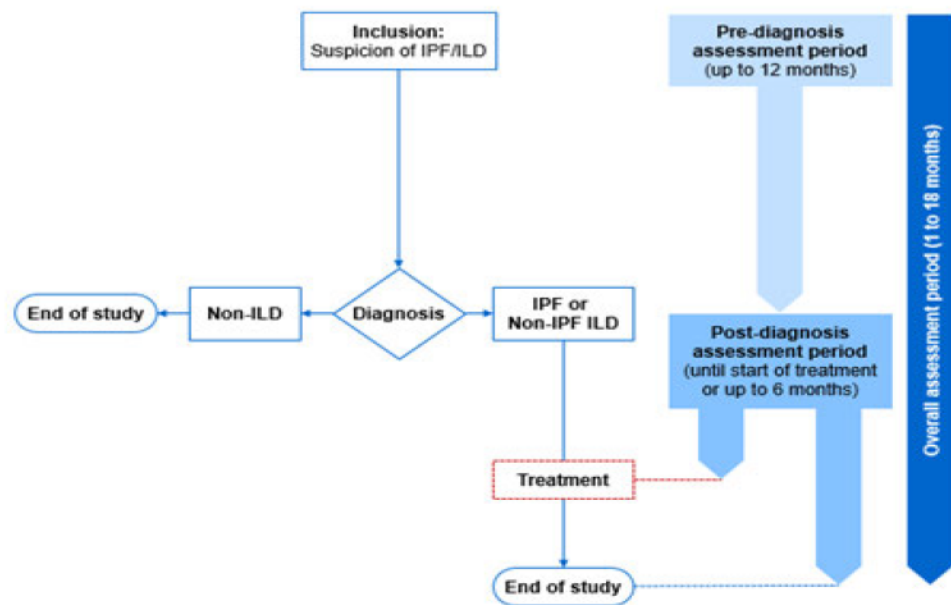
A patient will be eligible for inclusion if the Investigator has a suspicion that the patient may have IPF/ILD based on symptoms and radiological evidence. Investigators will discuss the benefits and risks of the study with the patient. The patient will subsequently be invited to participate in the study and to provide informed consent.

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” 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.

Patient management will be in accordance with local clinical practice and currently available guidelines.

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 the treatment commences. This includes the event of a patient receiving IPF or ILD drug treatment from a physician other than the investigator. The patient will be instructed to report such a treatment immediately to 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, DL_{CO}, 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 (see 9.4).

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.

At the enrollment visit, patients will receive training on the proper use of the devices from the study kit and the home based assessments and will be provided with a step-by-step manual helping them complete the spirometry assessments successfully. Visualizing their data on their tablets is thought to allow them to evaluate their condition and also to improve patient adherence to the study.

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 the inclusion in the study and afterwards just prior or at a scheduled site visit, 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 centers.

The study will provide a digital collaboration platform 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 centers 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.

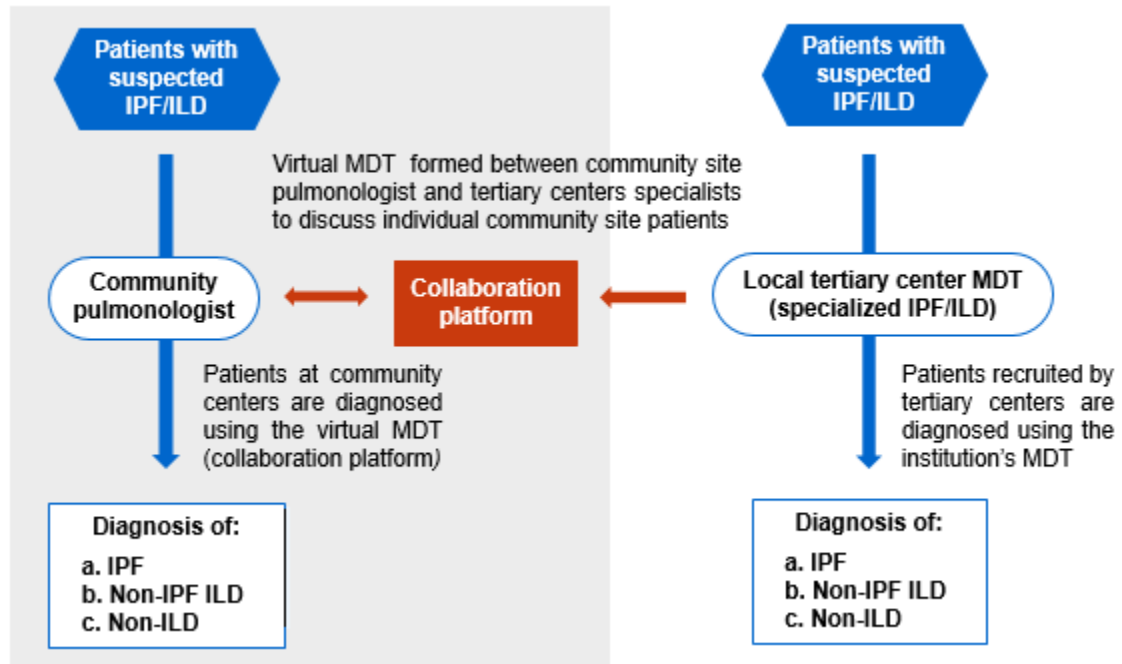
The use of the platform as a means of collaboration is not mandatory for participating sites. However, investigators will access the data from daily spirometry and accelerometry of their patients on the platform. Patient data will only be accessible by the treating physician (investigator) who can then decide to share them with the virtual MDT.

Home spirometry and accelerometry data will also be transferred from the patient tablet to the study database in an anonymized format, on a daily basis.

Investigator training will include training on the use of the collaboration platform.

The collaboration platform ("virtual" MDT) that will be used in this study is outlined in Figure 2.

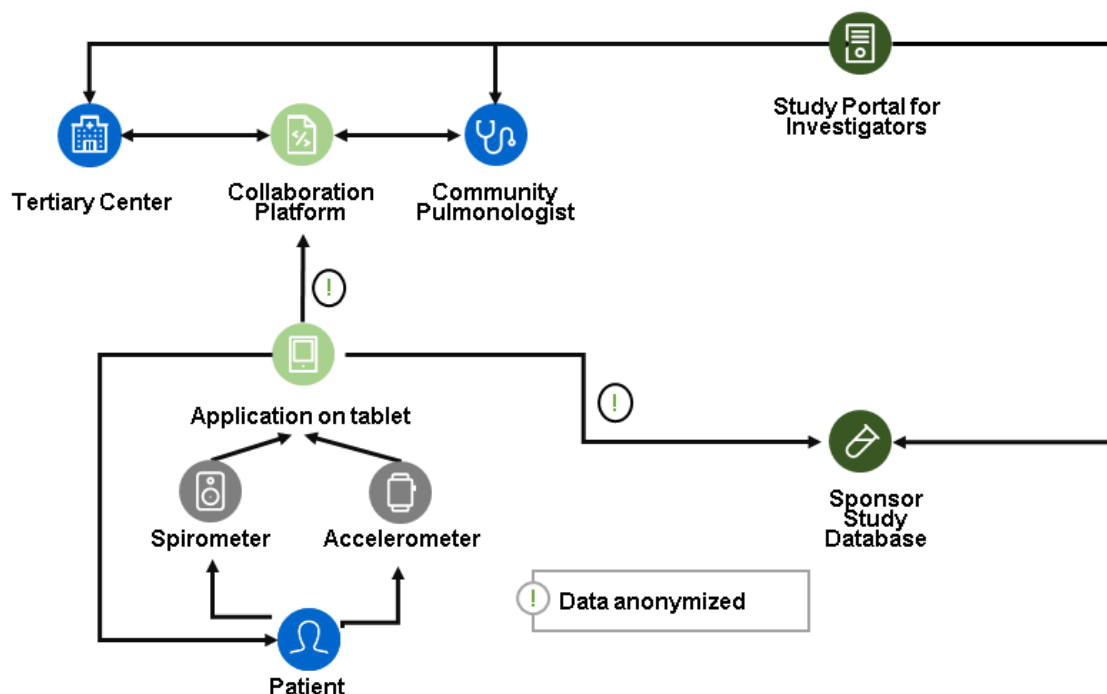
Figure 2 Collaboration Platform



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



The 'Study Portal for Investigators' is a repository for study documents, including the protocol, any manuals and study updates/newsletters. It will also provide the links to the collaboration platform and the eCRF.

3.2 End of Study and Length 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.

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 and depends on local clinical practice.

3.3 RATIONALE FOR STUDY DESIGN AND PATIENT POPULATION

This study will enroll patients with suspected IPF/ILD. In terms of current clinical practice, there is limited data available on the early course of disease and often clinicians require detailed information on disease behavior in order to establish a working diagnosis and to decide on further patient management. Therefore, a study following patients' lung function prior to diagnosis using handheld spirometry and subsequently relating these

data to levels of activity would provide useful and early information on disease progression.

This study will look into disease behavior in patients with suspected IPF/ILD. The study is meant to characterize the disease behavior of IPF and ILD and to detect potential differences in FVC decline between IPF and ILD.

By receiving data from daily handheld spirometry measurements, treating physicians may have an improved chance of detecting early a decline in lung function. Improving the ability of clinicians to detect early declines could potentially lead to improvements in both diagnosis and treatment for patients with IPF/ILD.

3.3.1 Rationale for Disease Response-based Endpoints

The primary objective for this study is to evaluate the change in pulmonary function (FVC measured in mL by daily handheld spirometry) from study inclusion to 6 months follow-up after a diagnosis of IPF or from study inclusion to the start of IPF drug treatment, chosen independently by the Investigator (whichever occurs sooner; see Section 2). Changes in FVC have been examined in several different clinical studies which enrolled patients with both IPF (du Bois et al. 2011a; Reichmann et al. 2015; Zappala et al. 2010) and non-IPF ILD (Solomon et al. 2013; Swigris et al. 2006; Zamora et al. 2008) and are generally accepted as a valid measure of disease course in patients with IPF/ILD. Moreover, in the single center study using handheld spirometry in 50 patients with IPF (Russell et al. 2016), the rate of decline in FVC following the use of handheld spirometers was highly predictive of outcome and subsequent mortality when measured at 3, 6, and 12 months. The conclusion of the study was that daily home spirometry measurements in patients with IPF are clinically highly informative and, for the majority of patients, quite easy to perform.

Other disease response-based parameters that will be examined in this study include accelerometry, 6MWT, and various PRO measures (K-BILD, mMRC, EQ-5D-5L, FAS and cough, urge to cough, and fatigue VAS). Some of these assessments have been used as disease response-based parameters in studies involving patients with IPF and ILD (Atkins et al. 2016; du Bois et al. 2011b; Nakayama et al. 2015; Nishiyama et al. 2010; Patel et al. 2012; Shulgina et al. 2013).

The PRO measures selected are short, easy to complete, covering various aspects of the disease. Moreover, fatigue has not been assessed by PROs in major IPF trials so far, despite the fact that fatigue is common and one of most limiting symptoms for patients. Thus, assessing fatigue by FAS in this trial will generate evidence that may be relevant for patients with IPF/ILD.

As diagnosis may influence health-related quality of life, the study will ensure that all PROs are repeated at the time of diagnosis and then analyzed separately for the time periods pre and post diagnosis.

4 MATERIALS AND METHODS

4.1 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. approximately 18 patients). Thus, approximately 72 patients with IPF and 90 patients with non-IPF ILD are planned 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.

4.1.1 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).

4.1.2 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.

4.2 Method of Treatment Assignment and Blinding

No investigational drug is involved in the study and therefore no treatment blinding will occur during the study.

4.3 Study Treatment

No investigational drug is involved in the study. During the study, patients will be managed according to the standard of care at the discretion of the Investigator.

4.4 Concomitant Therapy

Concomitant therapy consists of 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. All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All medications taken by the patient for concomitant disease(s) should be continued as necessary during the study and be recorded on the eCRF.

4.5 Study Assessments

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Enrollment Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Signed Informed Consent Forms for enrolled patients will be maintained at the study site file.

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant respiratory diseases, (asthma, chronic obstructive pulmonary disease, and pneumonia), reproductive status, smoking

history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications will be recorded as described in section 4.4.

Demographic data will include age, gender, and self-reported race/ethnicity (if country appropriate).

4.5.3 Physical Examinations (including vital signs)

Physical examinations will be conducted as per the schedule of activities (see Appendix 1). The directed physical examination should be based on signs and symptoms of the patient. Physicians should pay particular attention to the signs and symptoms that are characteristic of IPF or ILD. Additional physical examinations may be performed only if clinically indicated.

Physical examinations will include weight (kg); in addition, at baseline, the examination will include height (cm), and body mass index (BMI) will be calculated.

Physical examination is the responsibility of the principal Investigator or medically qualified designee.

4.5.4 Disease-relevant Assessments

Disease-relevant data potentially collected may include, but are not limited to, pulmonary function tests (FVC and DL_{CO}), physical functional capacity (6MWT and accelerometry data), and results from bronchoalveolar lavage (BAL), HRCTs, radiographs, and lung biopsy.

FVC will be conducted on site at each patient visit.

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

Patients will visit the site for assessment at baseline, diagnosis and end-of-study as well as at least once during each study period (pre- and post-diagnosis). During these visits HRCTs, radiographs, DL_{CO}, and lung biopsies may also be conducted and the results will be recorded.

Further information on the assessments (e.g., FVC, 6MWD, PROs) that will be conducted as part of this study can be found in the Procedure Manual.

4.5.5 Home-based Assessments

As described in section 3.1, at the enrollment visit, patients will receive training on the use of the components of the study kit – the spirometer, the accelerometer and the tablet computer.

The patients will be able to see the results of their daily spirometry and accelerometer readings presented graphically on the tablet computer. Data from the tablet will be automatically sent to the collaboration platform and eCRFs.

They will also receive sets of paper-based PRO questionnaires and scales for completion prior to site visits. These questionnaires can however also be completed on site, if the patient forgets to, or is otherwise unable to complete them at home before the visit.

4.5.5.1 Daily Spirometry

Throughout the study, patients will perform a spirometry reading 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.

4.5.5.2 Daily Physical Functional Capacity Assessments

Patient will be asked to wear an accelerometer which provides information on their physical activity, such as steps per day and calorie expenditure.

4.5.6 Laboratory and Other Biological Samples

No samples will be collected during this study for mandatory assessment of laboratory parameters or mandatory biomarkers.

4.5.7 Optional Biomarker Samples

The study is aiming to collect two optional baseline samples, only at sites where appropriate infrastructure is available. The following optional biomarker samples will be collected as per the Schedule of Assessments (see Appendix 1) and sent to the Sponsor or a designee for analysis:

- one serum sample (prepared from 8 mL of whole blood)
- one whole blood sample (6 mL)

The serum sample at baseline will be available for analysis of biomarkers that may be involved in the development and progression of IPF/ILD.

[REDACTED] Baseline protein biomarkers will also be examined to look for differences between patients with suspected IPF who later become diagnosed with IPF versus those who do not. Additionally, baseline protein biomarkers may be examined for correlations with other clinical outcomes measured such as activity and quality of life.

[REDACTED]

The whole blood sample will be collected at baseline for deoxyribonucleic acid (DNA) extraction to examine genetic polymorphisms and their potential role in the pathogenesis and associated clinical outcomes of IPF.

[REDACTED]

[REDACTED]

Patient participation for this assessment is voluntary, and declining participation to collect biomarker samples will not influence eligibility for this trial. Any samples remaining after analyses have been conducted will be destroyed no later than five years after the end of the study (see definition for End of Study in Section 3.2).

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

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome

and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

Data arising from sample analysis, including gene promoter polymorphisms, will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Patient-Reported Outcomes (PRO)

Various paper-based PRO questionnaires and visual analog scales 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 (Patel et al. 2012). The questionnaire consists of 15 items that are compiled into three domains of breathlessness and activities, psychological, and chest symptoms.
- **Modified Medical Research Council (mMRC) Dyspnea Scale.** The mMRC chronic dyspnea scale is simple to administer and has been used for many years to grade the effects of breathlessness on daily activities (Papiris et al. 2005). The scale consists of six categories about perceived breathlessness which range from no dyspnea (Category 0) to a very severe degree of dyspnea (Category 5).
- **The EuroQol 5-Dimension Questionnaire (EQ-5D-5L).** The 5-level version (EQ-5D-5L) is a validated self-report health status questionnaire (Brooks 1996; EuroQol Group 1990; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L:
 - a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
 - a VAS that measures health state.

- **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 (De Vries et al. 2004). A five-point scale (one for never to five for always) is used for patient responses and therefore 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 (Morice et al. 2007).

The above PRO questionnaires, translated, validated into the local language, will be completed in their entirety by the patients at baseline at the study site, and then just prior to or during their next scheduled site visit, following a request from the Investigator. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered prior to the patient receiving any information on disease status and prior to the performance of any non-PRO assessments. The questionnaires should always be completed in the same order.

Further information on these PRO assessments, which will be conducted as part of this study, can be found in the Procedure Manual.

4.6 Patient, Study, and Site Discontinuation

4.6.1 Patient Discontinuation from Study

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

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator. Patients who withdraw from the study will not be replaced.

4.6.2 Study Discontinuation

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

- Patient enrollment is unsatisfactory

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

4.6.3 Site Discontinuation

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

- Poor protocol adherence
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5 ASSESSMENT OF SAFETY

5.1 Safety Plan

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, as described in section 3.1.

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

It will be the responsibility of the Investigator to manage these events appropriately.

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.

6 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 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 is 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 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. 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 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.

6.2 Summaries of Conduct of Study

The number of patients who enroll, discontinue, or complete the study will be summarized by diagnosis cohort. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

A cohort of patients who could not be diagnosed during the first year after inclusion into the study will be analyzed separately as well.

6.3 Summaries of Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, sex and race (where permissible) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by diagnosis cohort.

A summary of concomitant medications will be displayed in frequency tables.

6.4 Primary and Secondary Analyses

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 with suspected to suffer from IPF.

6.4.1 Primary Endpoint

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 IPF), 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 entire study period. In addition, a single arm repeated measures mixed model will be applied to estimate the FVC decline over 6 months as a sensitivity analysis.

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.

6.4.2 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 fashion as the primary endpoint.

- The change in pulmonary function tests (mL and %predicted FVC) by site spirometry will be analyzed in the same fashion as the primary endpoint. Time adjusted mean changes and corresponding 95% confidence intervals will be provided for each diagnosis cohort.
- The change in 6MWT will be analyzed descriptively over time for each diagnosis cohort
- The change in physical functional capacity (measured by daily home accelerometry, e.g. number of footsteps per day and calorie expenditure) will be analyzed descriptively over time for each diagnosis cohort
- The change in PRO measures will be analyzed descriptively over time for each diagnosis cohort
- The correlation of FVC (mL) between home and site spirometry will be analyzed by calculating Pearson's correlation coefficient taking the individual mean FVC declines for each patient into account
- The correlation between physical functional capacity assessed at home in terms of the decline in the number of footsteps and on site in terms of the decline in distance of the 6MWT will be analyzed by calculating Pearson's correlation coefficient taking the individual values for each patient into account
- A comparison of disease behavior in IPF and non-IPF ILD patients will be summarized descriptively
- Evaluate the baseline characteristics of progressing vs non-progressing patients, patients requiring respiratory-related hospitalizations
- The incidence rate of non-elective hospitalization, both respiratory and all cause will be summarized descriptively by diagnosis cohort
- The incidence of Investigator-reported acute exacerbations will be summarized descriptively by diagnosis cohort
- Incidence of death, all cause and respiratory-related deaths will be summarized descriptively by diagnosis cohort
- The incidence of events related to the study assessments will be summarized descriptively by diagnosis cohort

6.4.3 Exploratory Efficacy Endpoints

- Different ILD subgroups, e.g. connective tissue disease associated ILD, chronic hypersensitivity pneumonitis ILD, will be analyzed in terms of baseline characteristics and change in FVC (ml) during the entire study period depending on the available data

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

Further details on the analyses on study cohorts and exploratory efficacy endpoints will be provided in the Statistical Analysis Plan.

6.5 Biomarker Analyses

Biomarker variables will be summarized using descriptive statistics: means/medians, standard deviation and range for continuous variables and frequency tables for categorical variables. Its relationship to primary and secondary endpoints may be explored. Details on these statistical methods will be provided in a separate statistical analysis plan.

6.6 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.

7 DATA COLLECTION AND MANAGEMENT

7.1 Data Quality Assurance

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) through the use of eCRFs (electronic case record forms). Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

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

7.2 Electronic Case Report Forms

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

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

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

7.3 Patient-Reported Outcome Data

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

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and study and system documentation will be archived. The Investigator will keep all PRO forms completed by the patient in the study records as source data. In addition, the site will receive all data in a machine-readable format on a compact disc. Acknowledgement of receipt of the compact disc is required.

7.4 Source Data Documentation

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medicotechnical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and Institutional Review Board (IRB)/Ethics Committee (EC) review. The study site must also allow inspection by applicable health authorities.

7.5 Use of Computerized Systems

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

7.6 Retention of Records

Records and documents pertaining to the conduct of this study, including but not limited to eCRFs, paper PRO data, Informed Consent Forms, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8 ETHICAL CONSIDERATIONS

8.1 Compliance with Laws and Regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 Informed Consent

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

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

8.3 Institutional Review Board or Ethics Committee

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

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

8.4 Confidentiality

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study Investigators or patients unless required by law. The aggregate results of any conducted research will be

available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

9 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 Study Documentation

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

9.2 Protocol Deviations

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

9.3 Site Inspections

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

9.4 Administrative Structure

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 50 sites globally will participate to enroll approximately 180 patients.

Central facilities will be used for biomarker analyses of baseline samples as specified in Section 4.5.

F. Hoffmann-La Roche Ltd

Protocol MA39297, Version 1, 26 April 2017

The study will be conducted under the leadership of a Steering Committee. The Steering Committee is composed of experts in the ILD field and members representing the Sponsor. The Steering Committee, together with the Sponsor, developed the study protocol and has overall responsibility for the study conduct and publication. A separate charter describing roles and responsibilities of the members of the committee will be maintained by the Sponsor.

9.5 Publication of Data and Protection of Trade Secrets

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

9.6 Protocol Amendments

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

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

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Appendix 1 Schedule of Activities

	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, DL_{CO}), 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 2

Hand-Held Spirometry: Example of Disease Behavior in an Individual Patient

Figure 4 shows the results of daily FVC measurements in a patient suffering a sudden and rapid decrease in FVC (Russell et al. 2016). This decrease may not have been detected the patient only been assessed using longer intervals between measurements.

Figure 4 Daily FVC Measurements over Time

