Official Title: Local Open-label Multicenter Study to Assess the Effectiveness of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis in Russian Clinical Practice

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PROTOCOL

TITLE:	**LOCAL OPEN-LABEL MULTICENTER STUDY TO ASSESS THE EFFECTIVENESS OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN RUSSIAN CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML39355
VERSION NUMBER:	2
TEST PRODUCT:	Esbriet / Pirfenidone (RO0220912)
MEDICAL MONITOR:	MD, PhD [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 2: See electronic date stamp below
DATE AMENDED:	Version 1: 17 January 2017

PROTOCOL AMENDMENT APPROVAL [redacted]

01.02.2019

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PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Pirfenidone (Esbriet) has been approved by the Ministry of Healthcare of the Russian Federation for the treatment of patients with IPF. In addition, inconsistencies within the protocol have been corrected.

The changes and associated rationales are described below, along with the sections of the protocol, which have been impacted. Similar changes have been made to the synopsis where applicable. Changes to the protocol, along with a rationale for each change, are summarized below in the table.

Change and Rationale	Sections Impacted
Pirfenidone was approved by the Ministry of Healthcare of the Russian Federation for the treatment of patients with IPF, that's why text of the Protocol ML39355 has been modified. Posology, schedule of administration, storage and handling are to be performed as prescribed in the official Russian instruction for use of pirfenidone (Esbriet). It also will be used as reference for a complete summary of safety information.	Section 1.2 Section 1.3.1 Section 3.3.1 Section 3.3.3 Section 4.3.1 Section 5.1 Section 5.7
Safety endpoint wording has been corrected to specify that change from baseline in clinical laboratory and ECG parameters will be assessed in the study (not limited to just findings).	Section 2
In the description of the study information about coordination of specialized centers work has been corrected. A Leading Specialist Investigator will coordinate their work.	Section 3.1
Clarification provided about the use of surgical lung biopsy samples (SLB) for the confirmation of IPF diagnosis. They will be used if performed prior enrolment in routine clinical practice.	Section 3.1
Also is clarified in the Description of the Study that not only radiological diagnosis of IPF but also histological diagnosis can be used along with clinical diagnosis to assess eligibility of	Section 3.1 Section 4.1.1

the patients. Inclusion criteria modified accordingly.	
The window ± 1 week for the end of the treatment with pirfenidone is set in the Protocol.	Section 3.1 Section 4.3.2
Figure 1 has been revised by addition of the text box to show when FVC and 6MWT will be performed according to the Schedule of Activities (Appendix 1).	Figure 1 in Section 3.1
The duration of participation in the study for an individual patient have been re-calculated taking in account windows for the visits and corrected from 27-30 weeks to 31-35 weeks as well as the duration of participation for the patients continuing in the rollover study (from up to maximum 56 weeks to maximum 58 weeks).	Section 3.2
Change in FVC in patients who will proceed with treatment in clinical practice over the more prolonged periods will not be evaluated after study completion because this is out of scope of this study. Text revised accordingly.	Section 3.3.5
Inclusion criteria 3 have been corrected so patients should have both “confident” or “consistent” with UIP diagnosis of IPF	Section 4.1.1
It has been clarified that patients must discontinue all prohibited medications at least 28 days before the start of treatment (instead of Screening).	Section 4.1.1
Exclusion criteria 3 revised so that if patient has relevant airways obstruction he will be excluded from the participation in the study	Section 4.1.2
Wording of exclusion criteria 7 revised. Patients with positive biomarker tests associated with the diseases mentioned in the exclusion criteria 7 also to be excluded from the participation in the study.	Section 4.1.2
The use of bronchodilator test at FVC measurement has been revised. It is obligatory only at screening. During further visits, bronchodilator test is not necessary to perform. Changes to	Section 4.5.7

the description of DLco measurement have been made accordingly.	
It has been clarified that ECG recordings must be performed before bronchodilator test (if scheduled).	Section 4.5.9
If any value of QTcF parameter during ECG recording is $>$ 500 ms and/ or $>$ 60 ms longer than the baseline value, another ECG must be recorded. Description of ECG recording revised.	Section 4.5.9
Description of the Borg Scale has been unified in accordance with the information provided in Appendix 4.	Section 4.5.11.1
Protocol has been revised to replace EuroQoL-5D Questionnaire by more detailed EuroQoL-5D-5L Questionnaire	Section 4.5.11.2 Section 6.4.2 Appendix 5
The sentence “Multidisciplinary team in each local centre must expect “confident” or “working” diagnose of IPF” has been removed because the use of such team is not to be performed during the study.	Section 4.5.13
In the Screening Period description has been clarified that In case of rescreening, the patient must be reconsented.	Section 4.5.13.2
Mistake in the text regarding the maximal duration of the screening has been corrected (it should be up to 28 days in accordance with Description of the Study and Schedule of Activities).	Section 4.5.13.2 Section 4.5.13.3
Information about when ECG should be done during the visits has been added to corresponding visit description.	Section 4.5.13.2 Section 4.5.13.3 Section 4.5.13.5 Section 4.5.13.8 Section 4.5.13.10

The obligation that all results of the Screening assessments and eligibility documentation will be submitted to the Sponsor or designee for approval has been removed from the protocol. Eligibility will be assessed by the investigator.	Section 4.5.13.2
Review of compliance and dispense supply of study treatment is not planned at certain visits (Week 12, 16 and 20). Text revised accordingly.	Section 4.5.13.6 Section 4.5.13.7 Section 4.5.13.8
It has been clarified that worsening of IPF (i.e. IPF progression) is considered as an AE only in case of fatal outcome attributed to this progression. In other cases exacerbation or worsening of IPF will not be recorded as AE.	Section 5.2.1 Section 6.4.3
Emergency Medical Contacts have been updated in the protocol.	Section 5.4.1
The subject samples of interest (populations) for the statistical analysis have been revised. One more sets added: the 'Full analysis' set (FAS).	Section 6
The level of confidence interval used for determination of sample size have been specified.	Section 6.1
Expected rate of screen failures (about 45%) have been specified in the protocol, so up to 109 patients will be screened for eligibility to include 60 subjects in the study.	Section 6.1
As in the study there is not specified 'safety' set a subject will be considered at risk if the subject is in the Treated set.	Section 6.2 Section 6.5
It has been clarified that the FAS set will be used for efficacy analysis.	Section 6.4
The distribution of primary outcome variable by patients will be provided in frequency table across three categories intead of two (category Decline of < 10% to 0% added).	Section 6.4.1

Discrepancy in the timelines for HRCT fibrosis score analysis and assessment of sign 'lung opacity' has been corrected. Optional HRCT is not planned to be done at Week 39, but at Week 26.	Section 6.4.3
In the study is not planned to include patients that are not able to sign the Consent Forms. Information about patient's legally authorized representative removed from the Protocol.	Section 8.2
Administrative structure information has been updated.	Section 9.4
List of the references has been updated. One reference moved from the text of the Protocol. Reference to EuroQol-5D Questionnaire removed. Reference to EuroQol-5D-5L Questionnaire added instead.	Section 10
The schedule of activities has been revised to reflect the changes to the protocol.	Appendix 1
Minor changes have been made to the text of HRCT Protocol (spelling mistakes and reference corrected)	Appendix 2
IPF Care Program has been revised to reflect the changes to the protocol. The scheme of IPF Care Program has been corrected accordingly.	Appendix 7

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS:

~~DMC~~	~~Data Monitoring Committee~~
~~ERS~~	~~European Respiratory Society~~
EP	*European Pharmacopeia*
ERS	*European Respiratory Society*
EQ-5D/ *EuroQol-5D*	European Quality of Life 5-Dimension Questionnaire
FAS	*Full analysis set*
FEV	*Forced expiratory volume*
SOC	System ~~орнфи~~ *organ* class
TNF	Tumor necrosis factor ~~inhibitors~~
USP	*United States Pharmacopeia*

SECTION 1.2 BACKGROUND ON PIRFENIDONE

Pirfenidone was first approved in Japan in 2008 under the trade name Pirespa. In 2011, Esbriet (pirfenidone) grabted marketing authorization in European Union (EU) as an orphan medicinal product for the treatment of adults with mild to moderate IPF. In 2014, the product was approved by the US FDA. Under different trade names pirfenidone is also approved for the treatment of IPF in many countries, including Argentina, China, India, Mexico and South Korea (Esbriet EMA 2010). Pirfenidone was also registered in Russia, marketing authorization number DP (drug product) - 004030. Pirfenidone (commercial product name Esbriet) was approved by *the* Mi~~s~~nistry of Health*care* of *the* Russian Federation for treatment of idiopathic pulmonary fibrosis.

SECTION 1.3.1 <u>Study Rationale</u>

Pirfenidone is currently approved for the treatment of patients with IPF in many countries worldwide, *including* ~~Registration in~~ Russia ~~is also expected~~. Despite the lack of epidemiological data on IPF in Russia, the number of patients diagnosed with the disease is expected to be large. The only available in Russia specific treatment of IPF

recommended by international guidelines is an antitumor agent nintedatib. At the stage of clinical development of pirfenidone, none of Russian clinical centers were ever involved in the programme of global clinical trials of the medicinal product, and experience with pirfenidone in clinical practice is absent. Therefore, there is a great unmet medical need for *a* local trial to estimate the effectiveness of pirfenidone in the Russian population suffering from IPF.

SECTION 1.3.2 Risk-Benefit Assessment

The estimated cumulative exposure to pirfenidone in clinical trials is from 3536 individuals. Up to the end of the most recent reporting period (27 February 2016), the majority of pirfenidone-treated patients are from the international phase III studies, mentioned in the Section 1.2. Cumulative post-marketing exposure to pirfenidone is estimated to be *over* 30 475 patient-years. A revised Periodic Benefit-Risk Evaluation Report (PBRER) submitted in 2016 updated the figure

SECTION 2. OBJECTIVES AND ENDPOINTS

TABLE 1: Objectives and Corresponding Endpoints

Table 1 has been revised to correct safety endpoint wording to specify that change from baseline in clinical laboratory and ECG parameters will be assessed in the study (not limited to just fundings). Titles for groups of endpoints have been added also.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	*Primary Efficacy Endpoints:*
To estimate the treatment effect of pirfenidone 2403 mg/d on lung function	Change from Baseline to Week 26 in absolute mL forced vital capacity (FVC) and % FVC.
Secondary Efficacy Objective:	*Secondary Efficacy Endpoints:*
To estimate the effectiveness of pirfenidone on IPF patients' functional capability and quality of life	• Change from baseline to Week 26 in 6-minute walk test (6MWT) distance • Change from baseline to Week 26 in patients' quality of life as measured with European Quality of Life 5-Dimension Questionnaire (EQ-5D)
Exploratory Efficacy Objective:	*Exploratory Efficacy Endpoints:*
To estimate the effectiveness of pirfenidone on the frequency and number of acute exacerbations of IPF and on features of HRCT	• Frequency and number of IPF exacerbations • CT scan evaluation (*semiquantitative assessment "HRCT fibrosis score". The high-resolution computed tomography (HRCT) findings will be*

	evaluated using HRCT scoring system. Interstitial lung disease (ILD) radiologist will make assessment of 4 main findings in three zones of each lung. The six zone scores will be averaged to determine the total score for each patient at baseline and at Weeks 26 and 52)
Safety Objective:	***Safety Endpoints***
To evaluate the safety of pirfenidone	• Treatment-emergent adverse events (AEs) • Treatment-emergent serious adverse events (SAEs) • Change from baseline in clinical laboratory ~~findings~~ *parameters* and electrocardiograms~~~~ *(ECG) parameters* ~~(ECGs)~~

SECTION 3.1 DESCRIPTION OF THE STUDY

Study sites will be specialized ~~referral~~ centres experienced in the management of IPF, and *their work* will be *coordinated* ~~represented~~ by a *Leading Specialist* ~~Coordinating~~ Investigator, chosen among experts in the field (see Section 9.4).

For enrolment into the study the diagnosis of IPF must be confirmed by central review of HRCT scans and of the surgical lung biopsy samples *(SLB)*, if available *(if performed prior enrolment in routine clinical practice)*. The HRCT scans will be reviewed by one or two central readers who are radiologists with expertise in IPF. If the first expert (central reader-1) agrees with the local opinion, the second expert (central reader-2) will not review scans. If the first expert disagrees with the local opinion, the second expert should review scans. Histopathological *(SLB)* samples will be reviewed by the one central reader who is a pathologist with expertise in IPF. Information on central reviewers and other administrative aspects of the study is provided in Section 9.4. All other diagnostic procedures will be performed and assessed at a local level.

Eligible patients aged 40–80 years must have a confident clinical and radiographic*/ or histological* diagnosis of IPF according to 2011 IPF guidelines (ATS 2011). Patients with possible UIP on high-resolution computed tomography and without ~~surgical lung biopsy~~ ~~(~~SLB~~)~~ in case of "working diagnose" of IPF during multidisciplinary team (MDT) discussion, are also eligible for the trial (see Table 2).

…

After the Screening, eligible patients will enter the Treatment period lasting 26 *(± 1)* weeks. All patients will receive pirfenidone 2403 mg/d administered orally in divided doses three times per day (TID) with food. Dose of the study treatment will be titrated over 14 days to the full dose of 9 capsules per day (three 267 mg capsules taken orally TID with food). Patients will remain on a stable maintenance dose for the duration of the

treatment period unless the dose is reduced to manage adverse events or titrated again when restarting study treatment after an appropriate interruption in treatment (see Section 5.1.2).

…

Treatment with pirfenidone will continue until Week 26 *(± 1)*. Patients will be followed through the Follow-up visit scheduled 2-4 weeks after treatment completion or until entry into the long-term follow-up (rollover study), whichever occurs earlier. Patients who undergo lung transplantation or who chose to withdraw from study procedures early will be followed for vital status until Week 26. If patients discontinue study treatment early for any reason, they should continue with all scheduled study procedures through Week 26.

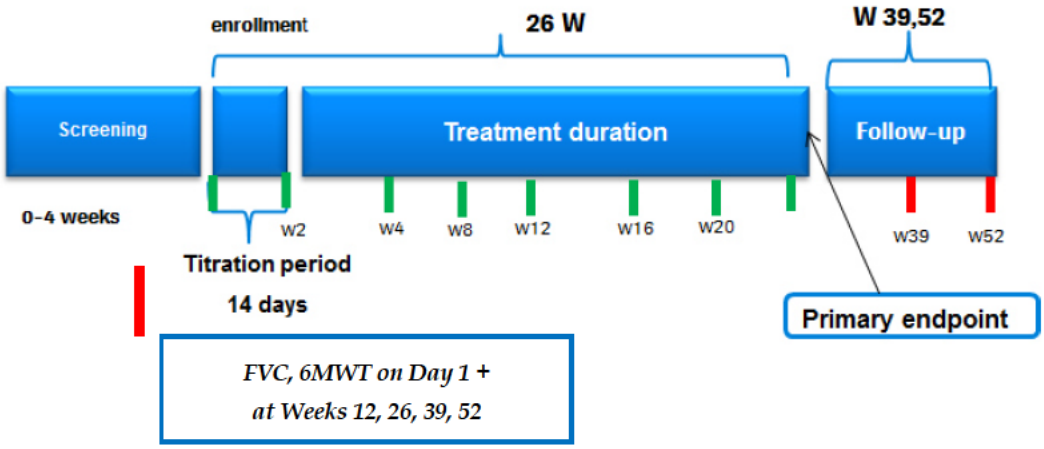
…

Patients who proceed until Week 26 in the study and are compliant with the study treatment, may continue treatment with commercially available pirfenidone after study completion in real clinical practice (long-term follow-up or rollover study). In this case, patients will have two follow-up assessments of FVC and 6MWD~~D~~*T* at Weeks 39 and 52 and CT scans evaluation at Week 52. Information on AEs occurance will also be collected during the rollover part of the study.

…

FIGURE 1: Study Schema

Figure 1 has been revised by addition of the text box to show when FVC and 6MWT will be performed according to the Schedule of Activities (Appendix 1).



…

An Independent Data Monitoring Committee (IDMC) will be implemented in the study. The IDMC will conduct regular review of the trial safety data, with the focus on death cases, serious adverse events, unexpected adverse events, adverse events leading to treatment or study discontinuation, liver enzyme increases, reported as adverse events, and other AEs immediately reported to the Sponsor (see ~~Section 5.2.3~~*Section 5.2.3.2*)

SECTION 3.2 End of Study and Length of Study

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The total length of the study, from recruiting of the first patient to the end of the study, is expected to be approximately 2 years. Duration of participation in the study for an individual patient is between ~~27~~*31* and ~~30~~*35* weeks (excluding long-term follow-up). For patients continuing in the rollover study the duration of participation in the study extends up to ~~56~~*58* weeks.

SECTION 3.3.1 Rationale for Pirfenidone Dose and Schedule

Posology and schedule of administration, including dose titration, of pirfenidone in the current study are *those* recommended *in the official Russian instruction for use of the IMP.* ~~unanimously by health authorities of countries where the product is approved for medical use, particularly in EU and the USA~~.

SECTION 3.3.3 Rationale for Control Group

The study is non-controlled by design. The choice of the non-controlled design is supported by the following positions:

- Enrolment of patients with rare disease in a clinical study is challenging and presumes ethical issues to be addressed in the design. Pirfenidone has been granted an orphan designation in Europe and the USA. Idiopathic pulmonary fibrosis is listed in the Russian Ministry of Healthcare registry of rare (orphan) diseases, so pirfenidone ~~is expected to get~~ *obtained* the status of an orphan drug in Russia, too.

- Efficacy of pirfenidone has been previously demonstrated in a number of placebo-controlled studies and meta-analyses, therefore, additional placebo-controlled study in patients with poor prognosis is deemed unethical.

- There is no adequate literature data to design a comparative active-controlled study of pirfenidone; non-inferiority study is merely feasible.

SECTION 3.3.5 Rationale for Endpoint Selection

…

~~In patients who will proceed with treatment in clinical practice after study completion, change in FVC over the more prolonged period of 12 months (52 weeks) will be evaluated. Thus, design features of the planned local clinical trial support the study objectives and are deemed to provide new insights in this modified study population.~~

...

The 2011 IPF guidelines provide updated and simplified IPF diagnostic criteria proposed by the ATS/ERS/JRS/ALAT, which may result in HRCT scanning playing a central role in the diagnosis of IPF. Technological advances in HRCT have brought *an* opportunity of HRCT as an accurate, sensitive and objective technique for evaluating IPF.

SECTION 4.1.1 Inclusion Criteria

…

3. Patients ~~could~~ *should* have both "confident" or "consistent" with UIP diagnosis of IPF based on clinical, radiologic *or* ~~and~~ pathologic data according to 2011 ATS/ERS guidelines at the Screening. HRCT scan performed within 24 months before the start of the Screening may be used~~, if it meets all image acquisition guidelines~~.

   …

8. Eligible patients must discontinue all prohibited medications at least 28 days before the ~~Screening~~ *start of treatment*.

SECTION 4.1.2 Exclusion Criteria

…

3. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC < 0.7) *at the Screening*.

   …

7. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/ dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis*, or patients with positive biomarker tests associated with these diseases (rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibodies) at the Screening*.

…

15. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:

    a. ~~d.~~ unstable angina pectoris or myocardial infarction

    b. ~~e.~~ congestive heart failure requiring hospitalization

    c. ~~f.~~ uncontrolled clinically significant arrhythmias

…

21. Use of any of the following therapies within 28 days before the start of treatment period:

    a. ~~f.~~ investigational therapy, defined as any drug that has not been approved for marketing for any indication in Russia

    b. ~~g.~~ any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, tumor necrosis factor (TNF)-α inhibitors, N-acetylcysteine (NAC), imatinib mesylate, interferon gamma-1b (IFN γ-1b), and tyrosine kinase inhibitors

    c. ~~h.~~ medications that are specifically used for the treatment of IPF including but not limited to angiotensin converting enzyme (ACE) inhibitors, colchicine, corticosteroids (prednisolone at doses exceeding 15 mg/day or equivalents), heparin, warfarin, and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication

    d. ~~i.~~ fluvoxamine

    e. ~~j.~~ sildenafil (chronic use for pulmonary arterial hypertension). Note: intermittent use for erectile dysfunction is allowed.

…

22. Any of the following liver function test outside specified limits at the Screening:

a. ~~d.~~ total bilirubin above the upper limit of normal (ULN);

b. ~~e.~~ aspartate or alanine aminotransferase (AST or ALT) > 3 × ULN;

c. ~~f.~~ alkaline phosphatase > 2.5 × ULN

23. Creatinine clearance < 30 mL/min, calculated using the Cockcroft-Gault formula (see ~~Section 4.5.7~~ *Section 4.5.8*)

SECTION 4.3.1 Formulation, Packaging, and Handling

…

Storage

~~Study treatment will be shipped to the investigational sites at room temperature and should be stored between 15 and 30oC. Study drug must not be refrigerated or frozen!~~

~~Shelf life is 3 years. Study drug must not be used beyond the expiration date.~~

Investigator is responsible for appropriate storage of the study drug. Investigator should maintain temperature in the room of storage and fill out temperature log on regular basis. *The study drug must be stored as prescribed in the official Russian instruction for use of pirfenidone (Esbriet).* ~~Do not store above 30°C.~~

Shelf life is indicated on label. Study drug must not be used beyond the expiration date.

Handling

Study treatment will be dispensed by the responsible investigator or investigational site pharmacist only to the participants of this clinical study. Drug accountability must be confirmed in written by the responsible employee of the site (see Section 4.3.3). Detailed Instructions for handling ~~and reconstitution~~ of the study drug will be provided to investigational sites as appropriate.

~~For further information on the formulation and handling of pirfenidone, see the latest version of the Investigator's Brochure or the pharmacy manual, if applicable.~~

SECTION 4.3.2 Dosage, Administration, and Compliance

Study treatment will be initiated on Day 1 in patients who completed Screening period successfully and fully comply for the study. *Study treatment will continue until visit at Week 26 (± 1 week), unless terminated earlier for reasons indicated in Section 4.6.2, or patient is proceeding in the rollover study.*

…

Any overdose or incorrect administration of the study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of the study drug should be recorded on the Adverse Event eCRF. ~~Section 5.3.5.11~~ *Section 5.3.5.10* summarizes available safety data related to overdosing of pirfenidone.

SECTION 4.3.3 Investigational Medicinal Product Accountability

…

Study treatment will be dispensed to the patient every 12 weeks, but may be dispensed at other visits, as needed. Patients will be instructed to store study treatment at room temperature. Patients will be instructed to use study treatments as prescribed by the investigator and to keep and return to the investigator all used and unused bottles of the study *drug* ~~treatment~~ *upon completion of the study treatment*.

SECTION 4.4.1 Permitted Therapy

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An acute IPF exacerbation is defined in updated publication (Collard HR et al*., 2016)* ~~Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 Aug 1)~~.

SECTION 4.5.6.1 High-Resolution Computed Tomography

HRCT scans should be obtained before the Screening period as part of the routine practice for a patient. It may be used to confirm eligibility~~, if they meet all of the image acquisition and quality criteria required by the central expert readers and separately for semiquantitative analysis of CT scans~~.

SECTION 4.5.7 Spirometry and DL_{CO} Measurements

FVC

…

At screening, ~~S~~*s*pirometry measurements of FVC will be performed before and after administration of albuterol (or salbutamol) from a metered dose inhaler. Four separate doses of 100 mg should be used when given by metered dose inhaler using a spacer. Tests should be repeated after a 15-min delay. *During further visits, bronchodilator test is not necessary to perform.*

DL_{CO}

DL_{CO} will be measured by determining the diffusing capacity of the lung for carbon monoxide corrected to hemoglobin. DL_{CO} measurement should be performed before or

at least 30 min after the last bronchodilator puff, *in case bronchodilator test has been performed.* It is measured by a single breath technique where helium and carbon monoxide are rapidly inspired, held for several seconds and then expired with the measurement of the remaining carbon monoxide. Comparison of the inspired and expired CO fractions allows calculation of DL_{CO} (Ranu et al. 2011).

SECTION 4.5.9 Electrocardiograms

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws*, bronchodilator test*) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

…

If at a particular postdose timepoint the ~~mean~~ QTcF is $>$ 500 ms and/ or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes or in the utmost 24 hours, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. A decision on study drug discontinuation should be made, as described in Section 5.1.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

SECTION 4.5.10 6-Minute Walk Test

The 6MWT measures the distance *in meters* that a patient can walk at his/her own pace on a measured, flat hard surface in a period of 6 min. The 6MWT assesses the global and integrated responses of all body systems involved during walking. The 6MWT based on ATS recommendations (ATS 2002) will be performed as outlined in the Reference Guide.

SECTION 4.5.11 Patient-Reported *and Clinician-Reported* Outcomes

SECTION 4.5.11.1 Borg Scale

The Borg Scale is an instrument to be self-administered by the patient as part of the 6MWT procedure (Borg 1982) (see Appendix 4). The Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, the patient should tick the answer to the questions: *"Please rate the current severity of your breathlessness by circling the most appropriate number*

on the following scale." ~~"Please grade your level of shortness of breath using this scale." and: "Please grade your level of fatigue using this scale."~~ At the end of the exercise, the patient should grade his breathing level ~~and level of fatigue~~ again.

SECTION 4.5.11.2 EuroQol 5-Dimension Questionnaire

The European Quality of Life (EuroQol) 5-Dimension Questionnaire, ~~3~~ *5*-level version (EQ-5D-5L), is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group, 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; Jindal et al. 2011; Behr J et al. 2013).

…

EQ-5D-5L questionnaire (Self-completed version on paper 1.0) will be used in the study. A sample of the validated questionnaire in English (for UK) is provided in Appendix 5. A validated version (Self-completed version on paper 1.0) in a local (Russian) language will be given to the patients for completion.

SECTION 4.5.13 ~~Detalization of~~ *Details on* the Study Visits

Before starting any study specific procedures, investigator must have HRCT and surgical biopsy (if applicable) performed in routine practice *confirming diagnose of IPF* to assess eligibility of patient. ~~Multidisciplinary team in each local centre must expect "confident" or "working" diagnose of IPF.~~

SECTION 4.5.13.1 Informed Consent Visit

Written informed consent must be obtained before initiating any study-associated procedures or changes to a pre-existing treatment regimen for purposes of this study. Informed Consent Visit *is* performed for explaining the study, collecting Informed Consent, handing out the Patient Information, collecting and sending HRCT or surgical biopsy (if applicable) and also for starting the washout medication prior 28 days to start of treatment. Any ~~identified~~ patient *identified* for the study, must discontinue all prohibited medications and stop smoking at least 28 days before *the* start of treatment. This is the Washout Period. If a medication must be tapered, tapering must start early enough that the patient has discontinued the drug 28 days before the start of treatment. Written informed consent must be obtained before withdrawing or tapering the patient off prohibited therapies.

After signing ~~of~~ *the* Informed consent, the investigator must review and transfer for central review HRCT scans, surgical lung biopsies (if available), which were performed in routine practice, to assess eligibility. (HRCT must be no older than 24 months. Results of the surgical lung biopsy must be no older than 4 years).

SECTION 4.5.13.2 Screening Period (Day -28 to Day -1)

Procedures conducted during Screening will be used to determine the eligibility of each patient for study enrollment before initiation of treatment and to establish patient baseline status. If patients fail Screening due to a condition that subsequently resolves (e.g., infection), they may be considered for rescreening; however, these patients must be discussed with the study *M*~~m~~edical *M*~~m~~onitor or designee before rescreening*. In case of rescreening, the patient must be reconsented.*

The Screening period is defined as the time between the date of the first Screening procedure and Day -1 and may last up to ~~49~~ *28* days. Screening procedures may be conducted on different days within the Screening period, if convenient. The order of procedures is not strict; however, basic requirements to be followed are given in gaps below.

The following procedures will be performed during Screening:

- Demographic data
- Review and update medical history and concomitant medications
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECGs (obtained before bronchodilator administration or on a separate day) All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, weight, and height
- Clinical laboratory assessments, including hematology, serum chemistries, serologic tests, and pregnancy test for women of childbearing capacity (blood samples must be drawn in fasted state)
- HRCT scan for baseline assessment (for patients with HRCT scans performed more than 2 months before the treatment period or with scans not meeting the imaging acquisition criteria outlined in Appendix 2)
- *Review transbronchial lung biopsy/ BAL;*
- ~~Unique triplicate ECGs (obtained before bronchodilator administration or on a separate day)~~
- Spirometry (FVC) (before and after bronchodilator administration with a 15 min delay). Collection and recording of the retrospective FVC values obtained in clinical practice over the last year.
- 6MWT and Borg Scale
- DL_{CO} (obtained before or 30 min after bronchodilator administration)
- GAP assessment
- Eliciting AEs

~~All results of the Screening assessments and eligibility documentation will be submitted to the Sponsor or designee for approval.~~

SECTION 4.5.13.3 Start of Treatment (Day 1)

Treatment must be initiated no more than ~~49~~ *28* days after the start of screening. All Day 1 procedures must be performed before administration of the study treatment. This study has no Day 0.

The following procedures will be performed on Day 1:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECGs. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity (blood samples must be taken in fasted state).
- ~~Unique triplicate ECGs (obtained before bronchodilator administration or on a separate day)~~
- Spirometry (FVC)
- 6MWT and Borg Scale
- Confirmation of patient eligibility for study participation
- Instruct the patient on how to titrate the dose of study treatment
- Dispense 12-week supply of study treatment. Dosing should start on the *D*~~d~~ay 1
- Dispense patient diary and instruct patients on how to properly record information using the diary.

SECTION 4.5.13.5 Weeks 2, 4, and 8 (± 2 Days)

The following procedures will be performed at Weeks 2, 4, and 8:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- *ECG (at Weeks 4 and 8 only)/ All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight
- ~~ECG (at Weeks 4 and 8 only)~~

- Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity (pregnancy test at Weeks 4 and 8 only)
- Review patient's diary

SECTION 4.5.13.6 Weeks 12 (± 2 Days)

The following procedures will be performed at Week 12:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity
- Spirometry (FVC)
- 6MWT and Borg Scale
- Review patient's diary
- ~~Review compliance and dispense 12 week supply of study treatment~~

SECTION 4.5.13.7 Weeks 16 and 20 (± 1 Week)

The following will be performed at Weeks 16 and 20:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity (pregnancy test at Week 20 only)
- ~~Collection of any unused study treatment, review compliance and dispensing of supply of study treatment, as needed~~
- Review and dispense new diary, if required.

SECTION 4.5.13.8 Week 26 (± 1 Week)

The following will be performed at Week 26 (on two separate days):

1st day at Week 26:

- Physical examination, vital signs
- Spirometry (FVC)
- 6MWT and Borg Scale

2nd day at Week 26:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECG. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity
- HRCT
- ~~ECG~~
- Spirometry (FVC) ~~(before and after bronchodilator administration with a 15 min delay)~~
- 6MWT and Borg Scale
- Collect patient's diary
- ~~Assessment of compliance~~

SECTION 4.5.13.10 Long-Term Follow-Up/ Rollover Study

Week 39 (± 2 weeks)

The following will be performed at Week 39:

- Physical examination, vital signs
- Clinical laboratory assessments (hematology, serum chemistries)
- Spirometry (FVC)
- 6MWT and Borg Scale
- Review AEs

Week 52 (± 2 weeks)

The following will be performed at Week 52:

- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECG. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs
- ~~ECG~~
- Clinical laboratory assessments (hematology, serum chemistries)

- HRCT
- Spirometry (FVC)
- 6MWT and Borg Scale
- Review AEs

SECTION 5.1 SAFETY PLAN

Pirfenidone is currently approved for medical use in many countries of the world (see Section 1.2). The safety plan for patients in this study is based on clinical experience with pifenidone in completed and ongoing clinical studies and in post-marketing use. The anticipated important safety risks for pirfenidone are outlined below. Please refer to the pirfenidone ~~Investigator's Brochure~~ *instruction for medical use of the medicinal product* for a complete summary of safety information.

SECTION 5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except *exacerbation or worsening of IPF* ~~as described in Section 5.3.5.10~~. *Worsening of IPF (i.e. IPF progression) is considered as an AE only in case of fatal outcome attributed to this progression (as described in Section 5.3.5.7)*.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)
- Lack of efficacy is not considered as AE

SECTION 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

…

- Requires or prolongs inpatient hospitalization (see ~~Section 5.3.5.10~~ *Section 5.3.5.9*)

SECTION 5.2.3.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be implemented in the study. All adverse events immediately reported to the Sponsor will be ~~expeditely~~ reviewed by the IDMC. The IDMC will also review every death case from the point of relationship to the study drug.

SECTION 5.4.1 Emergency Medical Contacts
Medical Monitor Contact Information for all sites

Medical Monitor :	[redacted], MD, PhD
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Roche Medical Responsible:	[redacted]
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

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

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

- Pirfenidone *Local Instruction for Use* ~~Investigator's Brochure~~
- Pirfenidone Core Data Sheet

SECTION 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

…

The main subject samples of interest are defined as follows.

The ‘Allocated to treatment’ set will consist of all subjects who:

- Gave their Informed Consent and
- Has successfully completed Screening procedures.

The ‘Treated’ set (TS) will consist of all subjects who:

- Were in the ‘Allocated to treatment’ set and

- Received any dose of the study treatment.

The 'Full analysis' set (FAS) will consist of all subjects who:

- *Were included in the 'Treated' set and*
- *Had data for at least one post-baseline assessment of any efficacy measurement.*

SECTION 6.1 DETERMINATION OF SAMPLE SIZE

The required sample size *for two-sided 95% confidence level* can be calculated using the following formula:

$$n = \hat{p}\hat{q}\left(\frac{Z_{\alpha/2}}{E}\right)^2;$$

$$n = 0.601 \times 0.399\left(\frac{1.96}{0.125}\right)^2 \approx 58.96.$$

Assuming previous calculations, 60 subjects included in the study will be sufficient for study parameters estimation. Taking into account study goals and the notion that the study drug is a product for the treatment of an orphan drug, margin of error of 0.125 is considered sufficient for parameter estimation. *For precision-based sample size justification, with a sample size of 60 patients, an expected mean value of 2.5% and standard deviation of 20, distance from the mean to limit of the two-sided 95% confidence interval for the mean Change from Baseline to Week 26 (Percent Predicted FVC) will extend about 5 (margin of error). The SD for change from baseline at week 26 is conservatively estimated based on the results of the ASCEND study as standard deviation for Percent Predicted FVC in pirfenidone group at week 26 (14.52) multiplied by √2 (Machin et al., 1997). This is also in line with the results of CAPACITY programme (Noble et al. 2011) in which the SD of changes from baseline was 17 - 20 at week 72.*

Taking into account an expected rate of screening failures about 45%, up to 109 patients will be screened for eligibility.

SECTION 6.2 SUMMARIES OF CONDUCT OF STUDY

…

Default Frequency Tabulations

For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) will be the default summary presentation.

For AEs and medical history, however, the denominator for the percentage calculation will be the number of subjects at risk. A subject will be considered at risk if the subject is in the *Treated* ~~safety~~ *set* ~~sample~~.

…

Handling missing values

For missing FVC data imputation, patients will be classified into different patterns depending on the availability of data:

Patients with a 26 week FVC value:

1. those who received ~~trial~~ *study* drug until 26 weeks;

2. those, who prematurely discontinued ~~trial~~ *study* drug, but who were followed up until Week 26.

SECTION 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race and ethnicity, height, weight, medical history, concomitant medication, serology etc) will be summarized using means, *SD* ~~standard deviations~~, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

SECTION 6.4 EFFICACY ANALYSES

The ~~Treated~~ *FAS* set will be used for the efficacy analysis.

All efficacy parameters ~~and~~ *will be* summarized with descriptive statistics (mean, *SD* ~~standard deviation~~, median, minimum maximum, 95% CI) for each measurement time point.

SECTION 6.4.2 Primary Efficacy Endpoint

…

The distribution (number and percentage) of primary outcome variable by patients across ~~two~~ *three* categories of change from Baseline (Decline of ≥10% or death before Week 26; *Decline of* < *10% to 0%;* Improvement of ≥ 0%) will be provided in frequency table.

SECTION 6.4.2 Secondary Efficacy Endpoints

…

Change from Baseline to Week 26 in patients' quality of life as measured with EQ-5D-*5L*

Results of EQ-5D-*5L* questionnaire will be summarized in two ways:

- Cross tabulation for each of five dimensions (Mobility, Self-Care, Usual Activities, Pain / Discomfort, Anxiety / Depression) by response and study week.
- VAS score, including changes from baseline, will be summarized with descriptive statistics (mean, standard deviation, median, minimum and maximum) for study week.

Additionally, a single ~~summary~~ *Index* score will be provided, if necessary.

SECTION 6.4.3 Exploratory Efficacy Endpoints

HRCT fibrosis score

The HRCT findings will be evaluated using HRCT scoring system. One ILD radiologist will make assessments of 4 main findings in three zones of each lung. The six zone scores will be averaged to determine the total score for each patient. Score will be recorded at the initial diagnosis and after six and 12 months in a similar manner for further comparison. The mean ± ~~standard deviation (~~SD~~)~~ of HRCT fibrosis score like continuous variable will be determined obligatory at baseline, 6 *months* and optional at 12 months.

The values of HRCT fibrosis score at baseline, at Week ~~39~~ *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

Additionally, the absolute change of HRCT fibrosis score from baseline at Week ~~39~~ 26 (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

The paired t-test will be performed to evaluate the changes in the variable from the baseline to Week ~~39~~ *26* (optional) and Week 52 (optional), respectively. The type I error rate will be set to 5%.

Lung opacity (ground-glass attenuation)

The sign 'lung opacity' will be qualified separately using methodology described above for other signs, and its change over time will be assessed outside the framework of a total summed index of fibrosis (HRCT fibrosis score). Lung opacity should be graded as

reticular abnormality to calculate the score for each zone, i.e. the percentage (%) area of opacity in a zone should be multiplied by the score of 2.

The percentage area of opacity at Baseline, at Week ~~39~~ *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

Additionally, the absolute change of percentage area of opacity from Baseline at Week ~~39~~ *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

Exacerbations

An exacerbation will be defined as an AE with special criteria, *i.e. only in case the exacerbation has led to death of a patient (see Section 5.2.1)*. Rate of exacerbation will be reported in three following tables:

SECTION 6.5 SAFETY ANALYSES

The ~~safety~~ *Treated set* ~~sample~~ will be used for the analysis of the safety and tolerability data.

Study treatment is defined as pirfenidone 2403 mg/d administered in divided doses ~~three times per day (~~TID~~)~~ with food. Study treatment will be titrated over 14 days to the full dose of 9 capsules per day (three 267-mg capsules taken orally TID with food). Patients will remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced to manage an AE or titrated again when restarting study treatment after a 28-day or greater interruption in treatment.

AEs will be reported on a per-subject basis, i.e. counting subjects rather than events. Only treatment emergent AEs will be reported. In the listings, however, all occurrences of the AEs will be presented.

Treatment emergent AEs will be summarized per primary *SOC* ~~system organ class~~ and *PT* ~~per preferred~~ term. Severity and drug-event relationship of treatment emergent AEs will be summarized separately.

Vital signs, including changes from baseline will be listed *and* summarized with descriptive statistics (mean, *SD* ~~standard deviation~~, median, minimum and maximum) for each measurement time point. Out-of-range values with assessment of clinical significance will be provided in frequency tables.

Results of ECG, including changes from baseline will be listed *and* summarized with descriptive statistics (mean, *SD* ~~standard deviation~~, median, minimum and maximum) for

each measurement time point. Out-of-range values with assessment of clinical significance will be provided in frequency tables.

Laboratory variables, including changes from baseline will be listed and summarized with descriptive statistics (mean, *SD* ~~standard deviation~~, median, minimum and maximum) for each measurement time point. Additionally, shift tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point will be provided.

SECTION 8.2 INFORMED CONSENT

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.

SECTION 9.4 ADMINISTRATIVE STRUCTURE

Sponsor:	F. Hoffmann-La Roche Ltd., Switzerland, *Representative Office of F.Hoffmann-La Roche Ltd.* Phone/ Fax: *Tel:* [redacted] / *Fax:* [redacted] Address: *Trubnaya sq., 2 "Neglinnaya Plaza" Business Center, 107031, Moscow, Russia*
Sponsor's Medical Monitor:	[redacted], MD, PhD IPHARMA LLC 5, Nobel str., Skolkovo, *143026*, Moscow, ~~143026,~~ Russia Tel.:+ 7 (495) 276-11-43 / Fax: + 7 (495) 276-11-47 [redacted]
Investigational Sites:	See ~~attached~~ *site* list
Coordinating Investigator:	[redacted] Doctor of Medical Sciences, Professor [redacted] [redacted], *Russia* Tel.: [redacted] / Fax: [redacted] [redacted]
Contract Research Organization:	Quintiles GesmbH, Representative Office in Russia, 37A-14 Leningradsky prospect, *125167,* Moscow, ~~125167,~~ Russia
Data Management:	Data Matrix Ltd ~~5 Kovenskiy per, 6 th floor~~*14 Nekrasova Street, Let. A, 191014,*

Saint Petersburg, ~~191014,~~ Russia

Tel.: +7 (812) 449-86-33 / Fax +7 (812) 449-86-35

info@dm-matrix.com

Central CT scan reviewers: [redacted], **MD, Professor.** [redacted]. Moscow

[redacted], **MD, Professor.** [redacted]

Central biopsy reviewers: [redacted] **MD, Professor.** [redacted], Moscow

[redacted], **Ph.D.** [redacted] Moscow.

SECTION 10. REFERENCES

…

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(3):265-275.

…

EuroQol Group [Web-source]. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-on-paper/

~~EuroQol Group, 1990. [Electronic source]. Access: http://www.euroqol.org/eq-5d-products/how-to-obtain-eq-5d.html Date 10 Oct 2016~~

Ichikado K, Suga M, Müller NL et al. *Acute interstitial pneumonia: C*comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med. 2002, 165:1551–6

…

Machin D., Campbell M., Fayers P., Pinol A. "Sample size tables for clinical studies"// Second edition Blackwell Science Ltd, 1997

…

APPENDIX 1: Schedule of Activities

The schedule of activities has been revised to reflect the changes to the protocol, including changes in Section 4.5.13 Detalization of the Study Visits.

Revised Appendix 1 provided below.

Appendix 1
Schedule of Activities

Study period	**IC visit**	**Screening (Washout, if applicable)**	**Treatment period**										**Follow-Up**	**Long-Term Follow-Up[16]**	
Week/ Day (Window)	-	–4 to –1 W	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 2 d)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Informed consent[1]	x														
Phone Call Assessment[2]				x											
Demographic data		x													
Medical history, concomitant medication[3]	x[3]	x[3]	x		x	x	x	x	x	x		x	x		
Vital signs, physical exam[4]		x	x		x	x	x	x	x	x	x	x	x	x	x
Height, weight[5]		x	x		x	x	x	x	*x*	*x*		x	*x*		

ECG[6]		x	x			x	x					x			x
~~Study drug dispense/ compliance[7]~~			~~x~~					~~x~~				~~x~~			
Eliciting AEs		x	x	x	x	x	x	x	x	x		x	x	x	x
Disease Assessment and PFT															
Review SLB[78] (if applicable)	x														
Review transbronchial lung biopsy/BAL[89]		x													
Review HRCT[78]	x														
HRCT		X[910]										x			x
Spirometry (FVC) ~~Collection and recording of the retrospective FVC values~~ [1011]		x	x					x			x	x		x	x
DLco		x													
6MWT		x	x					x			x	x		x	x
Laboratory Tests															
Hematology, blood chemistry[1142]		x	x		x	x	x	x	x	x		x	x	x	x

Serologic tests[11~~12~~]		x													

Study period	**IC Visit**	**Screening (Washout, if applicable)**		**Treatment period**										**Follow-Up**	**Long-Term Follow-Up[16]**
Week (Window)		–4 to –1	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 1 w)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Pregnancy test		x	X[12~~13~~]			x	x	x		x		x			
PROs and ClinROs															
GAP assessment		x													
Borg scale[13~~14~~]		x	x					x			x	x		x	x
EQ-5D questionnarie[13~~14~~]		x	x					x				x			x
Patient diary (review, dispense)[14~~15~~]		x	x	x	X	x	x	x	x	x		x			
Telephone calls (IPF Care program)[15~~16~~]															

[1] Written informed consent must be obtained prior to any study-associated procedure, including discontinuing any prohibited medications.

[2] Safety-related information (AEs) and adherence to treatment is collected.

[3] Complete medical history is collected at *an IC visit,* washout and screening only. Thereafter, directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary) is only collected.

[4] Complete physical examination is performed at the Screening only (head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems). At subsequent visits (or as clinically indicated), only limited, symptom-directed physical examinations should be performed.

[5] Height is assessed at the Screening only.

[6] ECG should be performed after patient's resting in a supine position for at least 10 min, prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws), bronchodilator administration and within 3 hours after any meal)

~~[7] Study treatment is dispensed to the patient every 12 weeks, but may be dispensed at other visits, as needed.~~

[7~~8~~] To confirm IPF will be applicable to use previously performed HRCT, if it *is* ~~meets image acquisition guidelines and~~ performed not earlier than 24 months before the Screening. Review of the SLB samples obtained within 4 years before the Screening should be performed centrally for eligibility confirmation. Histopathological evaluation, if not available, is not repeated at the Screening.

[8~~9~~] Transbroncheal biopsy or BAL are not mandatory and will only be reviewed at the Screening, if available, to exclude other causes of PF.

[9~~10~~] HRCT should be performed at the Screening only for patients having no validated procedure within 2 months prior initiation of treatment.

[10~~11~~] ~~On~~*At* screening, spirometry measurements of FVC should be performed before and after administration of albuterol (or salbutamol) from a metered dose inhaler (4 separate doses of 100 mg). Tests should be repeated after a 15-min delay. During further visits, bronchodilator test is not necessary to perform. Collection and recording of the retrospective FVC values obtained in clinical practice over the last year will be performed only ~~on~~ *at the* screening visit.

[11~~12~~] Blood samples must be drawn in fasted state. *Serologic tests: rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibody titer.*

[12~~13~~] Pregnancy test must be performed before first dosing on Day 1 and must be negative. If the urine test is positive, serum pregnancy test must be performed.

[13~~14~~] Questionnaires should be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, with the exception for Borg scale administered in conjunction with the 6MWT.

[14~~15~~] Patient diary should be filled out on daily basis by the patient and reviewed by the investigator at in-clinic visits. Patient diary captures information on compliance and AEs occurance

and is dispensed as needed.

[15~~16~~] Schedule of calls in IPF Care Program you can see in Appendix 7

[16] Only in patients continuing treatment with pirfenidone in real clinical practice.

APPENDIX 2: HRCT Protocol

Minor changes have been made to the text of Appendix 2 (spelling mistakes and reference corrected).

…

HRCT scans are usually obtained with the patient in supine position, with hands on the nape, in a single unforced breath hold. Scanning is normally directed upward (from feet to the head) in order to attenuate breathing artefacts in the basal parts of lungs. The key technical requirements are acquisition collimation ~~is~~ < 1 mm (opposite regular 0.65-0.8 mm), reconstruction parameters: 1 mm-slices, reconstruction interval 1 mm, high resolution imaging, lung window, imagin~~f~~g field is adjusted to the chest volume. Dose detection software should be utilized to decrease radiation exposure of the patients. Key technical requirements for spiral HRCT are summarized in the Table 1-1.

…

References

Ichikado K, Suga M, Müller NL et al. *Acute interstitial pneumonia:* ~~C~~*c*omparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002, 165:1551–6.

APPENDIX 5: EuroQol-5D-*5L* Questionnaire

Appendix 5 has been revised to replace EuroQoL-5D Questionnaire by more detailed EuroQoL-5D-5L Questionnaire (correct reference also provided accordingly).

Below samples of deleted EuroQoL-5D and introduced EuroQoL-5D-5L Questionnaire are presented.

EuroQol-5D Questionnaire

Questionnaire deleted

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

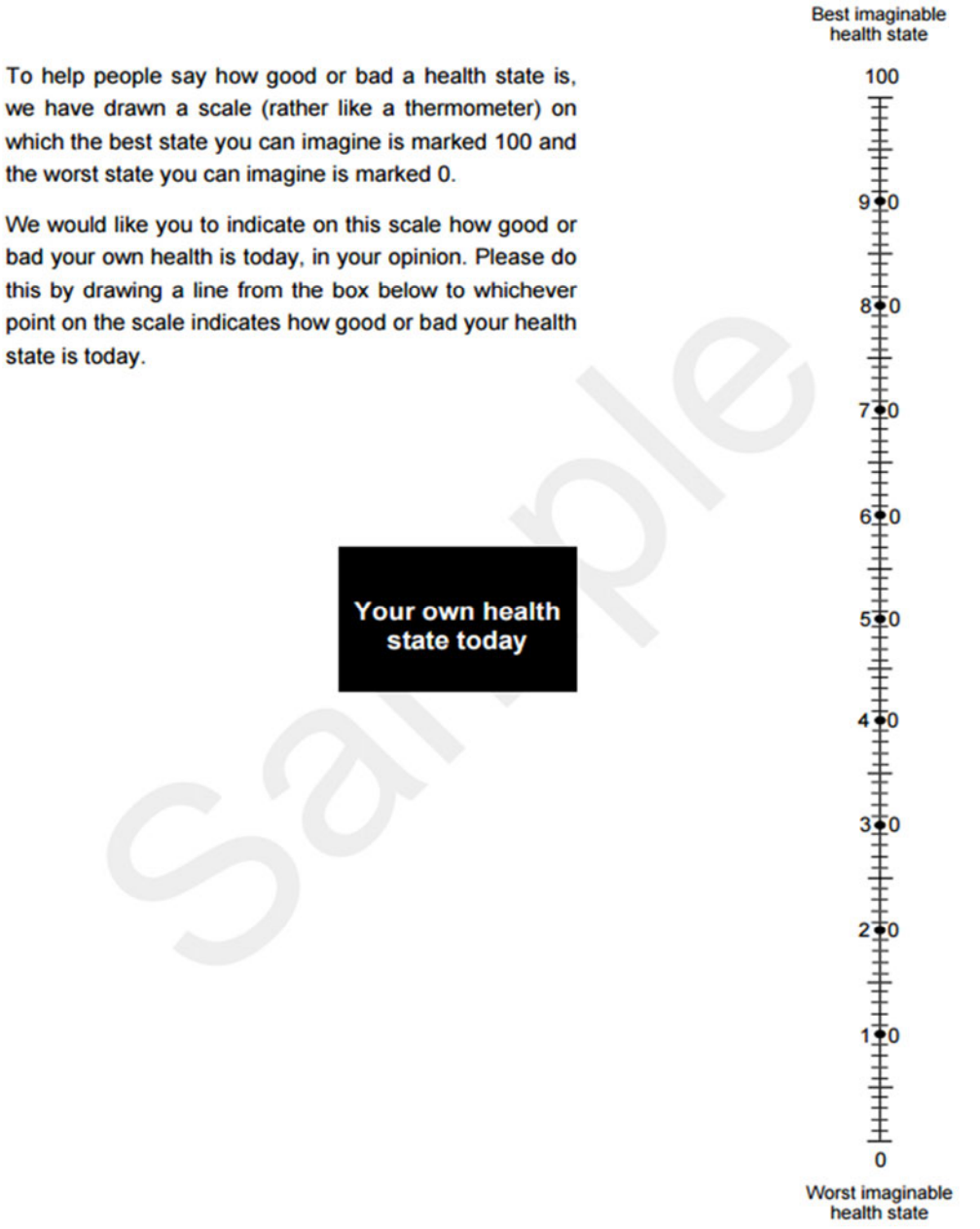
I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑



References

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

EuroQol-5D-5L Questionnaire

Questionnaire added

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 ❑

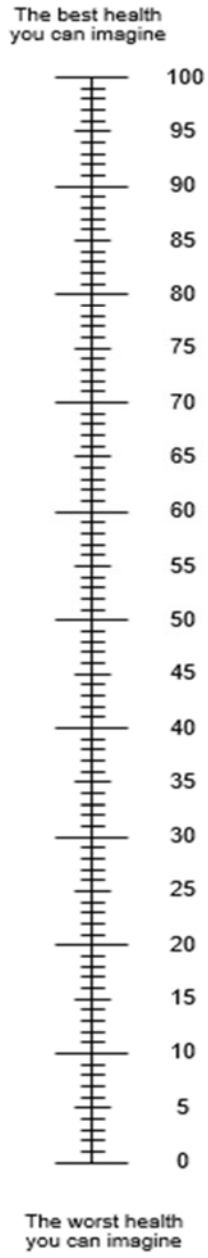
I am moderately anxious or depressed ❑

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 = ☐



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EuroQol Group. Web-source [Available at:https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-on-paper/]

APPENDIX 7: 7 IPF Care Program

Appendix 7 has been revised to reflect the changes to the protocol. The scheme of IPF Care Program has been corrected accordingly.

Previous version and revised version of the scheme of IPF Care Program are presented below.

Appendix 7

IPF Care Program

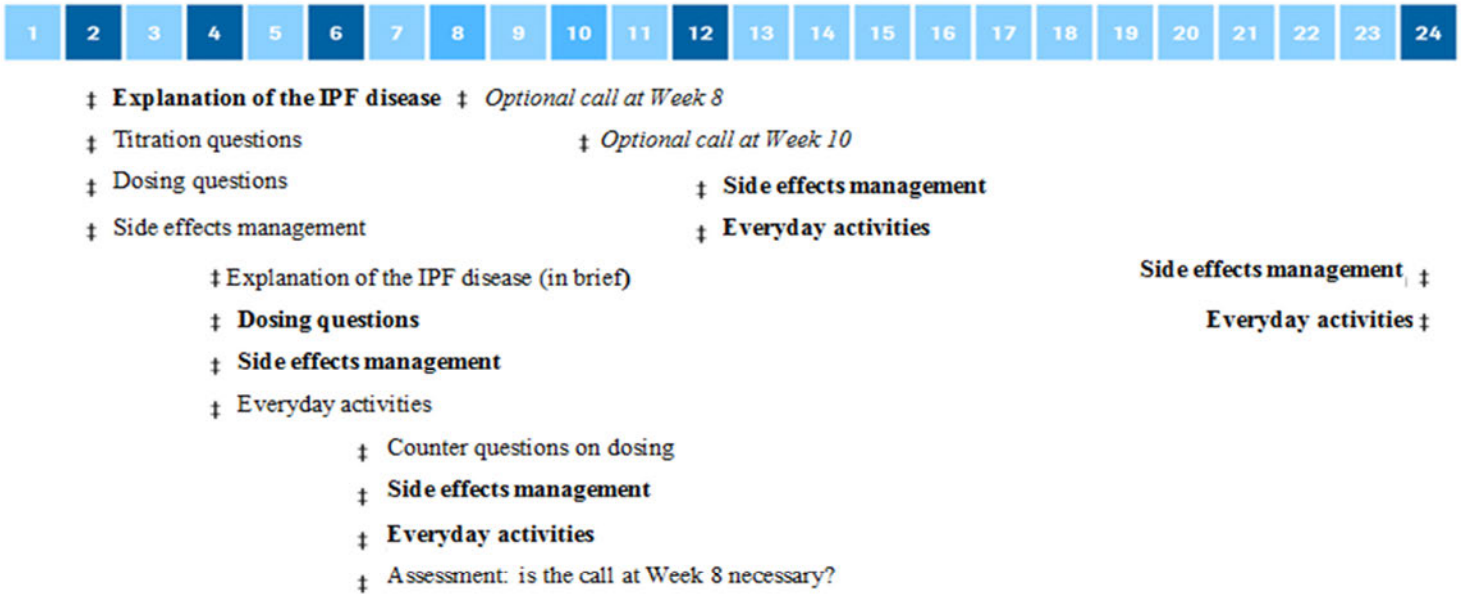
IPF Care Program by F. Hoffmann-La Roche Ltd (Switzerland)

Guidance for telephone calls to the patients participating in the clinical trial of pirfenidone

Telephone calls are scheduled at Weeks 3, 5, 7, 13 and 24. Optional calls can be performed at Weeks 8 and 10, if necessary.

A total number of calls is 5 to 7. Schedule of telephone calls and topics for discussion are detailed in the Figure below.

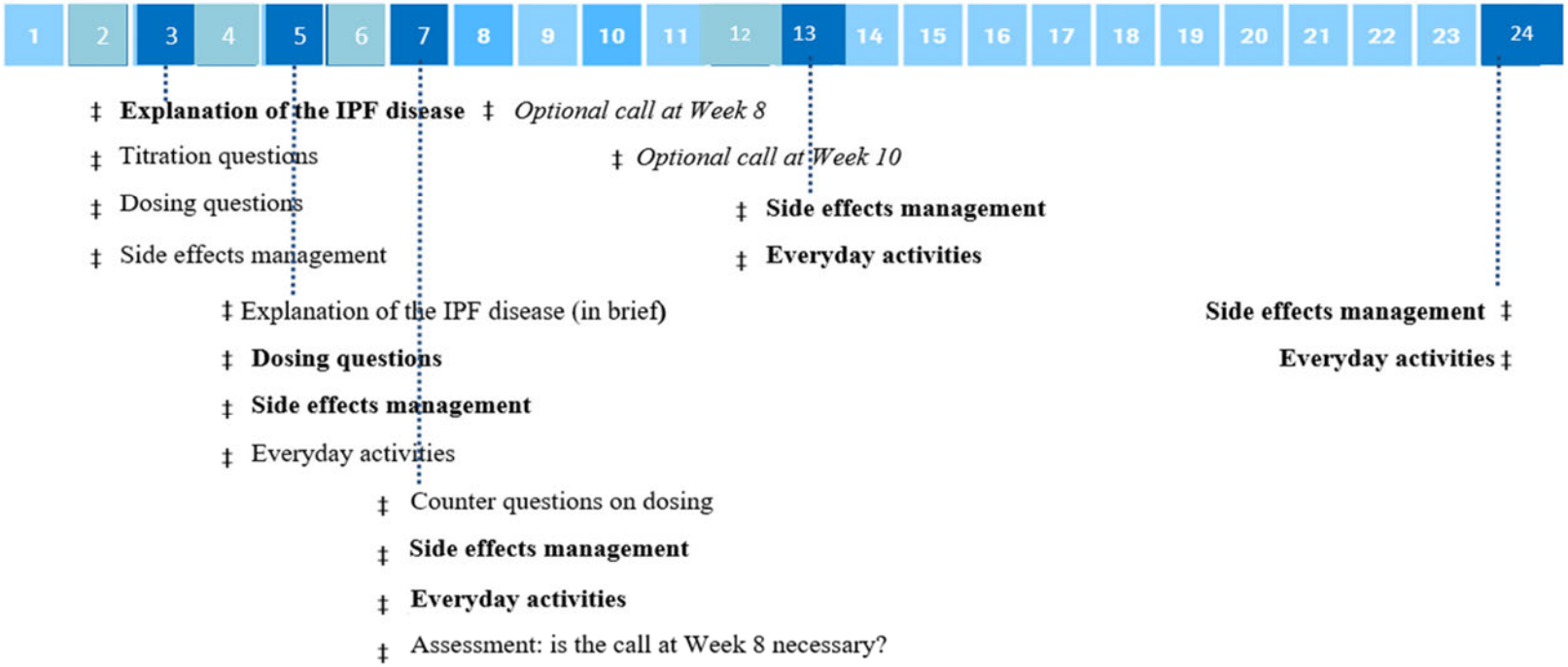
Scheme of IPF care Program (previous version) deleted



Answers to the questions in accordance with FAQ – IPF Care Program

A full version of the IPF Care Program will be supplied by the Sponsor to the investigators or other designated staff.

Scheme of IPF Care Program (current version) introduced



Answers to the questions in accordance with FAQ – IPF Care Program

A full version of the IPF Care Program will be supplied by the Sponsor to the investigators or other designated staff.

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TITLE:	**LOCAL OPEN-LABEL MULTICENTER STUDY TO ASSESS THE EFFECTIVENESS OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN RUSSIAN CLINICAL PRACTICE**
PROTOCOL NUMBER:	ML39355
VERSION NUMBER:	2
TEST PRODUCT:	Esbriet / Pirfenidone (RO0220912)
MEDICAL MONITOR:	MD, PhD [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

{Name}
{Address}

PROTOCOL

TITLE:	**LOCAL OPEN-LABEL MULTICENTER STUDY TO ASSESS THE EFFECTIVENESS OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN RUSSIAN CLINICAL PRACTICE**
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MEDICAL MONITOR:	MD, PhD [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	09 June 2018

FINAL PROTOCOL APPROVAL

Name: [redacted], [redacted] **Date:**

Signature

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Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of this form to the Sponsors or their designee. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE: **LOCAL OPEN-LABEL MULTICENTER STUDY TO ASSESS THE EFFECTIVENESS OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS IN RUSSIAN CLINICAL PRACTICE**

PROTOCOL NUMBER: ML39355

VERSION NUMBER: 2

TEST PRODUCT: Esbriet / Pirfenidone (RO0220912)

PHASE: III

INDICATION: Idiopathic Pulmonary Fibrosis (IPF)

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This is an interventional, open-label study to estimate effectiveness of pirfenidone in patients with idiopathic pulmonary fibrosis. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Corresponding Endpoints

Objectives	**Corresponding Endpoints**
Primary Efficacy Objective:	***Primary Efficacy Endpoint:***
To estimate the treatment effect of pirfenidone 2403 mg/d on lung function	Change from Baseline to Week 26 in absolute mL forced vital capacity (FVC) and % FVC.
Secondary Efficacy Objective:	***Secondary Efficacy Endpoints*:**
To estimate the effectiveness of pirfenidone on IPF patients' functional capability and quality of life	• Change from baseline to Week 26 in 6-minute walk test (6MWT) distance • Change from baseline to Week 26 in patients' quality of life as measured with European Quality of Life 5-Dimension Questionnaire (EQ-5D)
Exploratory Efficacy Objective:	***Exploratory Efficacy Endpoints:***
To estimate the effectiveness of pirfenidone on the frequency and number of acute exacerbations of IPF and on features of HRCT	• Frequency and number of IPF exacerbations • CT scan evaluation (*semiquantitative assessment "HRCT fibrosis score". The high-resolution computed tomography (HRCT) findings will be evaluated using HRCT scoring system. Interstitial lung disease (ILD) radiologist will make assessment of 4 main findings in three zones of each lung. The six zone scores will be averaged to determine the*

	total score for each patient at baseline and at Weeks 26 and 52)
Safety Objective:	***Safety Endpoints***
To evaluate the safety of pirfenidone	• Treatment-emergent adverse events (AEs) • Treatment-emergent serious adverse events (SAEs) • Change from baseline in clinical laboratory *parameters* and electrocardiogram *(ECG) parameters*

Study Design

Description of Study

This is a national, multicenter, interventional, non-randomized, non-controlled, open-label study to assess the effectiveness of pirfenidone in patients with IPF in Russian clinical practice. Approximately 60 patients will be enrolled to receive pirfenidone 2403 mg/d for 26 weeks. The primary endpoint will be the absolute change from Baseline to Week 26 in FVC (both in mL and % predicted). Eligible patients aged 40–80 years must have a "confident" clinical and radiographic*/or histological* diagnosis of IPF according to 2011 ATS/ERS IPF guidelines. Patients with "possible" usual interstitial pneumonia (UIP) on HRCT and without surgical lung biopsy (SLB) are also eligible for the trial in case the multidisciplinary team (MDT) of the investigator's site agrees on a "working diagnosis" of IPF. Patients with various degrees of lung function impairment can be included (%FVC ≥ 40; $\%DL_{CO}$ ≥ 30% and 6MWT ≥ 100 m). All chest HRCTs, and histopathology slides of surgical lung biopsies (the latter if available) will be centrally reviewed by experienced experts.

The study treatment will be initiated on Day 1 and continued until Week 26 *(± 1)*. The dose of study treatment will be titrated over 14 days. Patients will have a telephone assessment at Week 1 and an in-clinic assessment at Weeks 2, 4, 8, 12, 16, 20, 26. Patients should complete an adverse event and dosing compliance diary between all visits. If patients discontinue study treatment early for any reason, they should continue with all scheduled study procedures through week 26.

Patients who will pass 26 *(± 1)* weeks in the trial and continue treatment with pirfenidone in real clinical practice will have two follow-up assessments of FVC and 6MWD at Weeks 39 and 52 and CT scans evaluation at Week 52.

Number of Patients

Approximately 60 eligible patients with IPF will be enrolled into the study. *Expected rate of screening failure patients is about 45% which accounts for 109 patients to be screened.*

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Male and female patients aged 40–80 years, inclusive.
2. Clinical symptoms consistent with IPF of ≥ 6 months duration.
3. Patients *should* have both "confident" or "consistent" with UIP diagnosis of IPF based on clinical, radiologic *or* pathologic data according to 2011 ATS/ERS guidelines at the Screening. HRCT scan performed within 24 months before the start of the Screening may be used.
4. No features supporting an alternative diagnosis on transbronchial biopsy, bronchoalveolar lavage (BAL), or surgical lung biopsy, if performed. Results of the surgical lung biopsy performed within the last 4 years must be confirmed by central review.
5. Patients with %FVC ≥ 40 % at the Screening.
6. Patients with $\%DL_{CO}$ ≥ 30 % at the Screening.
7. Ability to walk ≥ 100 m during the 6-minute walk test at the Screening.
8. Eligible patients must discontinue all prohibited medications at least 28 days before the *start of treatment*.
9. Female patients of childbearing potential must have negative urine pregnancy test at the Screening and before first dosing on Day 1.
10. Patients able to conceive must agree to use safe contraceptive methods for the whole duration of the study and 28 days after the last dosing.
11. Ability to understand and sign Informed Consent Form.
12. Ability to comply with the study protocol, in the investigator's judgment (e.g. ability to fill out patient diary and other patient-reported outcome tools).
13. Able to understand the importance of adherence to study treatment and the study protocol and willing to follow all study requirements.

Exclusion Criteria

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

Disease-Related Exclusions:

1. Significant clinical worsening of IPF between the Screening and Day 1, in the opinion of the investigator.
2. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC < 0.7) *at the Screening*.
3. In the opinion of the investigator patients with predicted life expectancy <12 months or those who are on an active transplant waiting list.
4. Cigarette smoking within 28 days before the start of treatment or unwilling to avoid tobacco products throughout the study.
5. History of clinically significant environmental exposure known to cause pulmonary fibrosis (PF), including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds.

6. Known explanation for interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis, and cancer.
7. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/ dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis, *or patients with positive biomarker tests associated with these diseases (rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibodies) at the Screening.*
8. During baseline analysis of HRCT, significant coexistent emphysema (emphysema extent greater than extent of fibrosis) confirmed by central review.
9. Planned lung transplantation during the study.
10. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis.

Medical Exclusions:

11. Unable to perform 6MWT or to undergo pulmonary function test.
12. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 1 years. This does not include minor surgical procedures for localized cancer (e.g., basal cell carcinoma).
13. History of severe hepatic impairment or end-stage liver disease.
14. History of end-stage renal disease requiring dialysis.
15. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:
    a. unstable angina pectoris or myocardial infarction
    b. congestive heart failure requiring hospitalization
    c. uncontrolled clinically significant arrhythmias
16. Pregnancy or lactation, or intention to become pregnant during the study. Women of childbearing capacity are required to have a negative urine pregnancy test before treatment and must agree to maintain highly effective contraception.
17. History of alcohol or substance abuse in the past 1 year.
18. History of gastrointestinal (GI) tract perforation or history of peptic ulcer within six months.
19. Family or personal history of long QT Syndrome.
20. Known hypersensitivity to prior used pirfenidone or any excipient of the study treatment.
21. Use of any of the following therapies within 28 days before the start of treatment period:
    a. investigational therapy, defined as any drug that has not been approved for marketing for any indication in Russia
    b. any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene

antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, tumor necrosis factor (TNF)-α inhibitors, N-acetylcysteine (NAC), imatinib mesylate, interferon gamma-1b (IFN γ-1b), and tyrosine kinase inhibitors

c. medications that are specifically used for the treatment of IPF including but not limited to angiotensin converting enzyme (ACE) inhibitors, colchicine, corticosteroids (prednisolone at doses exceeding 15 mg/day or equivalents), heparin, warfarin, and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.

d. fluvoxamine

e. sildenafil (chronic use for pulmonary arterial hypertension). Note: intermittent use for erectile dysfunction is allowed.

Laboratory Exclusions:

22. Any of the following liver function test outside specified limits at the Screening:
    a. total bilirubin above the upper limit of normal (ULN);
    b. aspartate or alanine aminotransferase (AST or ALT) > 3 × ULN;
    c. alkaline phosphatase > 2.5 × ULN.
23. Creatinine clearance < 30 mL/min, calculated using the Cockcroft-Gault formula.
24. Electrocardiogram (ECG) with a QT interval corrected according to Fridericia's formula (QTcF) > 500 msec at the Screening.

Other Exclusions:

25. Inability to return for follow-up visits or obtain follow-up data required to assess study therapy, or presence of other reasons for anticipated non-compliance to therapy or procedures, in the opinion of the investigator.

End of Study

The end of study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or long-term follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur after 12 months after the last patient is enrolled.

Length of Study

The total length of the study, from recruiting of the first patient to the end of the study, is expected to be approximately 2 years. Duration of participation in the study for an individual patient is between *31* and *35* weeks (excluding long-term follow-up). For patients continuing in the rollover study the duration of participation in the study extends up to *58* weeks.

Investigational Medicinal Product

An investigational medicinal product (IMP) for this study is Pirfenidone (RO0220912) (INN: pirfenidone, ATC code L04AX05) 267 mg capsules, manufactured by Catalent Pharma Solutions

LLC, Winchester, USA. Pirfenidone is the medicinal product, immunodepressant, which has anti-inflamatory and antifibrotic effects. Pirfenidone is registered in Russia, marketing authorization number DP (drug product) - 004030. Pirfenidone (commercial product name Esbriet) was approved by the Ministry of Healthcare of the Russian Federation for treatment of idiopathic pulmonary fibrosis on 22-Dec-2016.

Permitted Therapy

Permitted therapy in the study include the use of corticosteroids either permanently at the discretion of the investigator as a part of routine management of IPF (at a maximum daily dose of 15 mg of prednisolone or equivalents), or temporally for the management of the IPF exacerbations without dose restriction for a period of up to 21 days.

Statistical Methods

Primary Analysis

The primary outcome variable will be analyzed in the *Full Analysis Set (FAS) sample (patients who were included in the 'Treated' set and had data for at least one post-baseline assessment of any efficacy measurement)*. The primary outcome variable is the absolute change in FVC from baseline to Week 26 (both in mL and % predicted). Baseline FVC will be the average of the highest FVC measurements recorded at the Screening and Day 1 visits. The FVC at Week 26 will be the average of the highest FVC measurements recorded on two separate days at week 26. Data will be analyzed using a standard descriptive statistics for continuous variables and 95% CI for the means.

For missing FVC data imputation, patients will be classified into different patterns depending on the availability of data. Patients with a 26-week FVC value will be classified into those who received study drug until Week 26 and those who prematurely discontinued but who were followed up until Week 26. Patients without a 26-week FVC value will be classified into those who were alive at Week 26 and those who died before Week 26. Missing data at other visits before Week 26 (primary outcome variable) will not be imputed.

Methods for handling missing data due to death will include replacement with the worst possible value (FVC = 0 mL or 0%) (primary analysis), replacement with worst observed FVC value at week 26 (sensitivity analysis), and replacement with an intermediate value (FVC =1500 mL or 50%) (sensitivity analysis).

Missing data due to reasons other than death will be replaced with imputed values based on the average measurements for "similar" patients at that time point (primary analysis). Similar patients are those without missing data before that time point and whose data have the smallest sum of squared deviations (SSD) from that patient for all visits prior to the one with the missing data. Missing data due to lung transplant will be imputed using the SSD method even if the patient dies after lung transplant. A sensitivity analysis will use the data imputed with last observation carried forward method (LOCF). Complete case analysis will also be performed as a sensitivity analysis.

The distribution (number and percentage) of primary outcome variable by patients across two categories of change from Baseline (Decline of ≥ 10% or death before Week 26; *Decline of < 10% to 0%;* Improvement of ≥ 0%) will be provided in frequency table. Absolute change in FVC from baseline at Weeks 12, 39 (optional) and 52 (optional) and mean FVC change through all time endpoints (both in mL and % predicted) will be summarized with standard descriptive statistics for continuous variables and 95% CI for means.

Determination of Sample Size

Taking into account the study design (single group prospective study), sample size was estimated based on feasibility of subject enrollment with precision-based approach. In the ASCEND study primary efficacy endpoint (Percent Predicted FVC) in pirfenidone group changed from 67.8 (11.24) (denoted as mean (SD)) at baseline to 65.3 (14.52) at week 26, with stable disease (decline in FVC < 10 % to 0 %) in 60.1% of study subjects.

Margin of error	Estimated % of endpoint	Required No of subjects
0.125	60.1	60

Assuming previous calculations, 60 subjects included in the study will be sufficient for study parameters estimation. Taking into account study goals and the notion that the study drug is a product for the treatment of an orphan disease, margin of error of 0.125 is considered sufficient for parameter estimation. *Taking into account an expected rate of screening failures about 45%, up to 109 patients will be screened for eligibility.*

Interim Analyses

Interim analysis is not planned.

SCHEDULE OF ACTIVITIES

Study period	**IC visit**	**Screening (Washout, if applicable)**	**Treatment period**										**Follow-Up**	**Long-Term Follow-Up[16]**	
Week/ Day (Window)		–4 to –1 W	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 2 d)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Informed consent[1]	X														
Phone Call Assessment[2]				x											
Demographic data		x													
Medical history, concomitant medication[3]	X[3]	x[3]	x		x	x	x	x	x	x		x	x		
Vital signs, physical exam[4]		x	x		x	x	x	x	x	x	x	x	x	x	x
Height, weight[5]		x	x		x	x	x	x	x	x		x	x		
ECG[6]		x	x			x	x					x			x
Eliciting AEs		x	x	x	x	x	x	x	x	x		x	x	x	x
Disease Assessment and PFT															
Review SLB[7] (if applicable)	x														
Review transbronchial lung biopsy/BAL[8]		x													
Review HRCT[7]	x														
HRCT		x[9]										x			x
Spirometry (FVC)[10]		x	x					x			x	x		x	x
Dlco		x													
6MWT		x	x					x			x	x		x	x
Laboratory Tests															
Hematology, blood chemistry[11]		x	x		x	x	x	x	x	x		x	x	x	x
Serologic tests[11]		x													

Study period	IC visit	Screening (Washout, if applicable)		Treatment period									Follow-Up	Long-Term Follow-Up[16]	
Week (Window)		–4 to –1	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 1 w)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Pregnancy test		x	X[12]			x	x	x		x		x			
PROs and ClinROs															
GAP assessment		x													
Borg scale[13]		x	x					x			x	x		x	x
EQ-5D questionnarie[13]		x	x					x				x			x
Patient diary (review, dispense)[14]		*x*	x	x	X	x	x	x	x	x		x			
Telephone calls (IPF Care program)[15]															

[1] Written informed consent must be obtained prior to any study-associated procedure, including discontinuing any prohibited medications.

[2] Safety-related information (AEs) and adherence to treatment is collected.

[3] Complete medical history is collected at *an IC visit*, washout and screening only. Thereafter, directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary) is only collected.

[4] Complete physical examination is performed at the Screening only (head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems). At subsequent visits (or as clinically indicated), only limited, symptom-directed physical examinations should be performed.

[5] Height is assessed at the Screening only.

[6] ECG should be performed after patient's resting in a supine position for at least 10 min, prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws), bronchodilator administration and within 3 hours after any meal)

[7] To confirm IPF will be applicable to use previously performed HRCT, if it is performed not earlier than 24 months before the Screening. Review of the SLB samples obtained within 4 years before the Screening should be performed centrally for eligibility confirmation. Histopathological evaluation, if not available, is not repeated at the Screening.

[8] Transbroncheal biopsy or BAL are not mandatory and will only be reviewed at the Screening, if available, to exclude other causes of PF.

[9] HRCT should be performed at the Screening only for patients having no validated procedure within 2 months prior initiation of treatment.

[10] *At* screening, spirometry measurements of FVC should be performed before and after administration of albuterol (or sa butamol) from a metered dose inhaler (4 separate doses of 100 mg). Tests should be repeated after a 15-min delay. During further visits, bronchodilator test is not necessary to perform. Collection and recording of the retrospective FVC values obtained in clinical practice over the last year will be performed only *at the* screening visit.

[11] Blood samples must be drawn in fasted state. *Serologic tests: rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibody titer.*

[12] Pregnancy test must be performed before first dosing on Day 1 and must be negative. If the urine test is positive, serum pregnancy test must be performed.

[13] Questionnaires should be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, with the exception for Borg scale administered in conjunction with the 6MWT.

[14] Patient diary should be filled out on daily basis by the patient and reviewed by the investigator at in-clinic visits. Patient diary captures information on compliance and AEs occurance and is dispensed as needed.

[15] Schedule of calls in IPF Care Program you can see in Appendix 7

[16] Only in patients continuing treatment with pirfenidone in real clinical practice.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
ATS	American Thoracic Society
AV	Atrioventricular
BAL	Bronchoalveolar lavage
CI	Confidence interval
CK	Creatine kinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DL_{CO}	*Carbon monoxide diffusing capacity*
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EP	*European Pharmacopeia*
ERS	*European Respiratory Society*
EU	European Union
EQ-5D/ *EuroQol-5D*	European Quality of Life 5-Dimension Questionnaire
FAQ	Facts, Answers, Questions
FAS	*Full analysis set*
FDA	Food and Drug Administration
FEV	*Forced expiratory volume*
FOV	Field of vision
(F)VC	(Forced) Vital capacity of the lungs
GAP	Gender, Age, Physiology (multidimensional index and staging system for IPF)
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
Hb	Hemoglobin
hERG	Potassium ion channel of myocytes, coded with hERG gene
HIV	Human immunodeficiency virus

Abbreviation	Definition
HMG-CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A
(HR)CT	(High-resolution) Computer Tomography
HU	Hounsfield unit
IC_{50}	Half inhibitory concentration
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN γ	Interferon gamma
IMP	Investigational Medicinal Product
ILD	Interstitial lung disease
IND	Investigational New Drug (application)
INN	International non-proprietary name
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
kV	Kilovolt
LDH	Lactic dehydrogenase
LL	Left lung
LOCF	Last observation carried forward
LPLV	Last patient, last visit
LPS	Lipopolysaccharide
(n)MET	N-minute exercise test
MDT	Multidisciplinary team
mEq/L	Milliequivalents per liter, equivalent to mmol/L
(n)MWT	N-minute walk test
NAC	N-acetylcysteine
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
PBRER	Periodic Benefit-Risk Evaluation Report
PFS	Progression-free survival
PFT	Pulmonary function test
PK	Pharmacokinetic
PRO	Patient-reported outcome
PT	Preferred term
QTc(F)	QT interval corrected (using Fridericia's formula)
RBC	Red blood cells

Abbreviation	Definition
RL	Right lung
RR	Risk ratio
SAE	Serious Averse Event
SD	Standard deviation
SOC	System *organ* class
SSD	Sum of squared deviations
SLB	Surgical lung biopsy
SpO_2	Oxygen saturation
TID	Three times per day
TGF	Transforming growth factor
T_{max}	Time to reach maximal concentration of the drug in plasma
TNF	Tumor necrosis factor
TS	Treated set
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
US	United States of America
USP	United States Pharmacopeia
UV	Ultraviolet
VAS	Visual Analogue Scale
WBC	White blood cells
yr	Year

1. BACKGROUND

1.1 BACKGROUND ON IDIOPATHIC PULMONARY FIBROSIS

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown etiology that is characterized by progressive fibrotic destruction of the lung (predominantly of the lung interstitium), resulting in disabling dyspnea, poor gas exchange, decrease in lung volume, progressive pulmonary insufficiency typically leading to death. IPF is recognized by the American Thoracic Society (ATS) and European Respiratory Society (ERS) 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 histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) (ATS 2011).

IPF is a rare disease, it is estimated to affect about 1-5 in 10,000 persons in the European population (Orphanet). IPF is most prevalent in middle aged and elderly patients, and usually presents between the ages of 40 and 70 years (Esbriet EMA 2010); the mean age at presentation is 66 years (Orphanet). Although the disease is idiopathic by its nature, several potential risk factors have been identified. They include cigarette smoking, environmental exposures (metal, wood dust and other dusts), microbial agents (Epstein-Barr virus, cytomegalovirus, human herpesvirus), gastroesophageal reflux and genetic factors (ATS 2011).

Usual clinical findings of IPF include slowly increasing dyspnea and a nonproductive cough with progressive loss of lung volumes, i.e. decreased forced vital capacity (FVC), and decline in exercise tolerance. On high-resolution computed tomography (HRCT) scan, there are peripheral (subpleural), bibasilar, reticulonodular abnormalities with architectural distortion, honeycomb change, and traction bronchiectasis (ATS 2011; ATS 2015).

The diagnosis of IPF carries a bleak prognosis, the median survival for IPF patients is about 3 years from the time of diagnosis. However, the course of the disease varies from patient to patient. Slow progression of respiratory insufficiency is interspersed with episodes of acute exacerbation that accelerate decline and may be fatal (Collard et al. 2007).

For the long period of time no preventive approach or globally accepted treatment other than lung transplantation and enrolment in clinical trials was available. There is no good evidence to suggest the efficacy of therapies often administered to patients with IPF, such as corticosteroids and azathioprine (ATS 2015; Walter et al. 2006). ATS/ERS/JRS/ALAT guidelines updated in 2015 gave conditional positive recommendations for two antifibrotic drugs for the treatment of IPF - nintedanib and pirfenidone (ATS 2015).

1.2 BACKGROUND ON PIRFENIDONE

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is a small non-peptide molecule of low molecular weight (185.2 daltons). Pirfenidone belongs to immunosuppressants group (ATC code L04AX05). The mechanism of action of pirfenidone has not been fully established, but existing data suggest that it exerts both antifibrotic and anti-inflammatory properties (Esbriet EMA 2010). Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors.

Pirfenidone was first approved in Japan in 2008 under the trade name Pirespa. In 2011, Esbriet (pirfenidone) grabted marketing authorization in European Union (EU) as an orphan medicinal product for the treatment of adults with mild to moderate IPF. In 2014, the product was approved by the US FDA. Under different trade names pirfenidone is also approved for the treatment of IPF in many countries, including Argentina, China, India, Mexico and South Korea (Esbriet EMA 2010). Pirfenidone was also registered in Russia, marketing authorization number DP (drug product) - 004030. Pirfenidone (commercial product name Esbriet) was approved by *the* Ministry of Health*care* of *the* Russian Federation for treatment of idiopathic pulmonary fibrosis.

Nonclinical development

In the *in vitro* experiments pirfenidone suppressed the proliferation of fibroblasts, inhibited lipopolysaccharide (LPS)-stimulated release of platelet-derived growth factor AB and of transforming growth factor (TGF)-β1, inhibited collagen synthesis in fibroblast cultures and promoted the release of collagenase from fibroblasts over the concentration range 5.5 to 185 µg/mL. These *in vitro* effects were observed at clinical concentrations or low multiples of clinical concentrations. *In vivo* studies were conducted in relevant models of fibrosis in mice, rats, hamsters and dogs. Pharmacodynamic activity was demonstrated particularly in bleomycin-induced lung fibrosis in mice, rats and hamsters (Esbriet EMA 2010).

In safety pharmacology studies pirfenidone demonstrated minimal hERG inhibition (16%) at concentration of 185 µg/mL, with a half inhibitory concentration (IC_{50}) of 925 µg/mL (5000 µM). Other cardiovascular effects in rats included decreased blood pressure and increased heart rate observed at doses 30-300 mg/kg. Premature ventricular contractions and atrioventricular (AV) block occurred at submaximal and maximal doses. In dogs prolongation of QT and corrected QT (QTc) intervals was seen at 100 mg/kg, shortening of QT interval and increase in heart rate were observed at 300 mg/kg (Esbriet EMA 2010).

Pharmacokinetics of pirfenidone was similar in mice, rats, guinea pigs and dogs. The compound was rapidly absorbed after oral administration with time to maximal

concentration (t_{max}) of 0.5 hour. Terminal elimination half-life ranged between 1.6 to 4.8 hours in mice, rats and dogs, and was similar to that in humans. Bioavailability was 97% in rats and 79% in dogs. In mice and rats pirfenidone showed an approximately dose-proportional increase in absorption in the dose range 30 to 2000 mg/kg. In humans serum protein binding, predominantly to albumin, ranged from 54% to 62% (Esbriet EMA 2010).

There is little evidence to suggest accumulation of pirfenidone and its metabolites in any tissues. Metabolism of pirfenidone was rapid in rats and dogs and was mediated mostly by CYP1A2 enzymes in humans. The major circulating metabolite was 5-CA pirfenidone, its plasma levels approximated a half of parent compound levels in dogs and humans. The elimination of pirfenidone was rapid and occurred primarily via the urine as the 5-CA pirfenidone metabolite. About 5 to 15% of the metabolite was excreted faecally. No meaningful changes in pharmacokinetics were seen with repeated dosing (Esbriet EMA 2010).

Toxicity of pirfenidone was studied after single dosing in mice, rats and dogs, and after multiple dosing in mice and rats. Toxic effects were more pronounced in fasted animals than in fed. In rodents, effects on the central nervous system, including hypoactivity, respiratory effects, abnormal gait and recumbency, were noted. Emesis, salivation and vocalisation were observed in dogs. These signs developed after administration of high doses (1000 mg/kg). The main target organ was liver, however, the changes were considered to be adaptive. There was no irreversible or delayed toxicity (Esbriet EMA 2010).

The main signs in the oral subchronic and chronic toxicology studies of pirfenidone lasting up to 6-9 months were similar to those seen acutely. The exposure at the highest doses in rats and dogs were 6- and 12-fold, respectively, the C_{max} in IPF patients. Animals developed altered posture, hypoactivity, altered gait and sedation. The main systemic effect was an increase in liver weight, often in conjunction with hepatic centrilobular hypertrophy. There was no increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin, suggesting that the hepatic effects were not a manifestation of toxicity, but the result of enzyme induction. All findings were completely or partially reversible. There was no evidence of delayed toxicity. The no observed adverse effect level (NOAEL) in the 3- and 9-month studies was established as 200 mg/kg/day (Esbriet EMA 2010).

Pirfenidone was shown to cause phototoxicity and photoirritation when dosed concomitantly with exposure to ultraviolet (UV) light in hairless mice. Pirfenidone was not antigenic in guinea pigs and was not immunotoxic. Pirfenidone had no harmful effect on fertility of rats of either gender, but there was an effect on the oestrous cycle in females. There were also a prolongation of gestation and reduction in viability in

the neonates in animals dosed in the perinatal period. The NOAEL for fertility and fetal development was 900 mg/kg/day (Esbriet EMA 2010).

Pirfenidone and its 5-CA main metabolite were not genotoxic in a standard battery of tests. Tumours were found in the carcinogenicity studies after oral administration via diet to mice at doses of 800, 2000 or 5000 mg/kg/day for 104 weeks. However, tumors in the liver were deemed to result from the adaptive changes and not indicative of a risk for humans. Hormonally-mediated mechanisms were proposed for tumours in the uterus of rats; but the findings were not considered to represent a risk to patients (Esbriet EMA 2010).

Clinical studies

Efficacy, safety and tolerability of pirfenidone were studied in four phase III, multicentre, randomized, double-blind, placebo-controlled studies in patients with IPF (King et al. 2014; Noble et al. 2011; Taniguchi et al. 2010).

SP3 study

275 Japanese patients with IPF and mild to moderate impairment in pulmonary function tests (PFT) were randomized in 2:1:2 ratio to pirfenidone 1800 mg/day, 1200 mg/day or placebo, respectively, for 52 weeks. The primary end-point was the change in vital capacity (VC) from baseline to week 52. Other end-points were progression-free survival (PFS) time and the change in the lowest oxygen saturation (SpO_2) during the 6-minute steady-state exercise test (6MET). The progression of disease was defined by death and/ or ≥ 10% decline in VC from baseline. The trial demonstrated a benefit to both doses of pirfenidone in terms of a reduction in VC decline (-0.09 L vs. -0.16 L; P = 0.0416). Significant improve in PFS was observed for the high-dose group (P = 0.028). Marginally significant difference with placebo was found for the low-dose group (P = 0.066). There were no significant differences in the mean changes of the lowest SpO_2 and incidence of acute exacerbation during the study or within 28 days after the termination of the study among the three groups (Taniguchi et al. 2010).

CAPACITY -004 and -006 studies

In two concurrent trials (CAPACITY-004 and -006) patients with IPF were randomly assigned to pirfenidone or placebo for a minimum of 72 weeks in 110 centres in Australia, Europe, and North America. In study 004, 435 patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo. In study 006, patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The primary endpoint was change in percentage predicted forced vital capacity (FVC) at week 72.

In study 004, pirfenidone significantly reduced decline in FVC with mean change at week 72 -8.0% (standard deviation [SD] 16.5) in the pirfenidone 2403 mg/day group and -12.4% (18.5) in the placebo group (difference 4.4%, 95% CI 0.7 to 9.1). 35 (20%) versus 60 (35%) patients, respectively, had a decline of at least 10%. Mean change in FVC in the lower dose pirfenidone group was intermediate to that in the higher dose pirfenidone and placebo groups.

In study 006, the difference between groups in FVC change at week 72 was not significant (P = 0.501). Mean change in FVC at week 72 was -9.0% (SD 19.6) in the pirfenidone group and -9.6% (19.1) in the placebo group (difference 0.6%, 95% CI -3.5 to 4.7). However, a consistent pirfenidone effect was apparent until week 48 and in an analysis of all study timepoints. Fewer overall deaths and fewer deaths related to IPF occurred in the pirfenidone 2403 mg/day groups than in the placebo groups (Noble et al. 2011).

ASCEND study

555 patients were randomized in 1:1 ratio to receive pirfenidone 2403 mg/day or placebo for 52 weeks (King et al. 2014). The primary endpoint was the change in FVC or death at week 52. In the pirfenidone group, as compared with the placebo, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10% or more in the percentage of FVC or who died. There was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P < 0.001). Pirfenidone significantly reduced the decline in the 6-minute walk distance (6MWT) (P = 0.04) and improved PFS (P < 0.001). There was no significant difference in dyspnea scores or in rates of death from any cause or from IPF. However, in a prespecified pooled analysis incorporating results from CAPACITY trials, the between-group difference favoring pirfenidone was significant for death from any cause (P = 0.01) and from IPF (P = 0.006). Pooled results suggested improved mortality with pirfenidone (risk ratio [RR], 0.70; 95% CI, 0.47–1.02; moderate confidence). Pirfenidone reduced the rate of FVC decline (standardized mean difference, 0.23; 95% CI, 0.06–0.41; high confidence) (King et al. 2014).

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and PFS in patients with IPF (King et al. 2014).

In addition, an open-label long-term extension RECAP study enrolled patients, who completed CAPACITY and ASCEND trials (Costabel et al. 2014). The primary objective of RECAP study was to assess safety and tolerability of pirfenidone in the long-term treatment of IPF. Secondary objective was to obtain additional efficacy data for pirfenidone 2403 mg/day in patients who previously were allocated to placebo in CAPACITY and ASCEND trials and received pirfenidone in RECAP study for the first time. Preliminary results of the study demonstrated that patients newly treated with

pirfenidone in RECAP had similar FVC and survival outcomes to those in the CAPACITY pirfenidone group (Costabel et al. 2014).

Refer to the latest version of the Investigator's Brochure for details on nonclinical and clinical studies.

On the basis of evidence from the Phase III ASCEND and CAPACITY studies, joint clinical guidelines published in 2015 by ATS/ERS/JRS/ALAT recommendation put a high value on the potential benefit of pirfenidone on patient-reported outcomes (PROs), disease progression, as measured by rate of forced vital capacity decline, and mortality, and a lower value on potentially significant adverse events.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

IPF is a life-threatening and severely debilitating disease characterized by poor survival. Results from five controlled clinical trials, as described above, suggest that treatment with pirfenidone results in clinically meaningful benefits in a variety of domains, including lung volume (FVC/VC), exercise tolerance (change in 6MWT distance), PFS and risk of mortality.

Pirfenidone is currently approved for the treatment of patients with IPF in many countries worldwide*, including* Russia. Despite the lack of epidemiological data on IPF in Russia, the number of patients diagnosed with the disease is expected to be large. The only available in Russia specific treatment of IPF recommended by international guidelines is an antitumor agent nintedatib. At the stage of clinical development of pirfenidone, none of Russian clinical centers were ever involved in the programme of global clinical trials of the medicinal product, and experience with pirfenidone in clinical practice is absent. Therefore, there is a great unmet medical need for *a* local trial to estimate the effectiveness of pirfenidone in the Russian population suffering from IPF.

1.3.2 Risk-Benefit Assessment

The estimated cumulative exposure to pirfenidone in clinical trials is from 3536 individuals. Up to the end of the most recent reporting period (27 February 2016), the majority of pirfenidone-treated patients are from the international phase III studies, mentioned in the Section 1.2. Cumulative post-marketing exposure to pirfenidone is estimated to be *over* 30 475 patient-years. A revised Periodic Benefit-Risk Evaluation Report (PBRER) submitted in 2016 updated the figure.

Results from five controlled clinical trials suggest that treatment with pirfenidone is generally safe and well tolerated. Patients from both CAPACITY studies who were assigned to receive high-dose pirfenidone reported increased rates of nausea,

dyspepsia, vomiting, anorexia, photosensitivity, and rash compared with placebo (Noble et al. 2011). Similar results were observed in the ASCEND trial in regards to gastrointestinal (GI) and skin-related adverse events. Pooled analysis showed increased rates of photosensitivity (high confidence), fatigue (moderate confidence), stomach discomfort (moderate confidence), and anorexia (high confidence) in patients treated with pirfenidone. However, those events rarely led to treatment discontinuation (King et al. 2014).

According to RECAP study interim data, 603 patients were exposed to pirfenidone. Mild to moderate gastrointestinal (nausea, dyspepsia and diarrhoea) and skin-related events (rash, photosensitivity reaction) were among the most commonly reported adverse events. The incidence of nausea was 16.8 per 100 patient-years and of rash 8.2 per 100 patient-years (Costabel et al. 2014).

The data show that treatment with pirfenidone is associated with acceptable adverse events profile, and the benefit in patients with IPF outweighs the potential risks. Thus, pirfenidone represents an appropriate treatment option for patients with idiopathic pulmonary fibrosis.

2. OBJECTIVES AND ENDPOINTS

This study will estimate effectiveness of pirfenidone in patients with idiopathic pulmonary fibrosis. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	*Primary Efficacy Endpoint:*
To estimate the treatment effect of pirfenidone 2403 mg/d on lung function	Change from Baseline to Week 26 in absolute mL forced vital capacity (FVC) and % FVC.
Secondary Efficacy Objective:	*Secondary Efficacy Endpoints:*
To estimate the effectiveness of pirfenidone on IPF patients' functional capability and quality of life	• Change from baseline to Week 26 in 6-minute walk test (6MWT) distance • Change from baseline to Week 26 in patients' quality of life as measured with European Quality of Life 5-Dimension Questionnaire (EQ-5D)
Exploratory Efficacy Objective:	*Exploratory Efficacy Endpoints:*
To estimate the effectiveness of pirfenidone on the frequency and number of acute exacerbations of IPF and on features of HRCT	• Frequency and number of IPF exacerbations • CT scan evaluation (*semiquantitative assessment "HRCT fibrosis score". The high-resolution computed tomography (HRCT) findings will be evaluated using HRCT scoring system. Interstitial lung disease (ILD) radiologist will make assessment of 4 main findings in three zones of each lung. The six zone scores will be averaged to determine the total score for each patient* at baseline and at Weeks 26 and 52)
Safety Objective:	*Safety Endpoints*
To evaluate the safety of pirfenidone	• Treatment-emergent adverse events (AEs) • Treatment-emergent serious adverse events (SAEs) • Change from baseline in clinical laboratory *parameters* and electrocardiogram *(ECG) parameters*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a local, multicenter, interventional, non-randomized, non-controlled, non-comparative, open-label study to assess the effectiveness of pirfenidone in patients with IPF in Russian clinical practice. Approximately 60 patients diagnosed IPF will be enrolled to receive pirfenidone 2403 mg/d for 26 weeks. No comparator group is implied in the study.

Study sites will be specialized centres experienced in the management of IPF, and *their work* will be *coordinated* by a *Leading Specialist*-- Investigator, chosen among experts in the field (see Section 9.4).

For enrolment into the study, the diagnosis of IPF must be confirmed by central review of HRCT scans and of the surgical lung biopsy *(SLB)* samples, if available *(if performed prior enrolment in routine clinical practice).* The HRCT scans will be reviewed by one or two central readers who are radiologists with expertise in IPF. If the first expert (central reader-1) agrees with the local opinion, the second expert (central reader-2) will not review scans. If the first expert disagrees with the local opinion, the second expert should review scans. Histopathological *(SLB)* samples will be reviewed by the one central reader who is a pathologist with expertise in IPF. Information on central reviewers and other administrative aspects of the study is provided in Section 9.4. All other diagnostic procedures will be performed and assessed at a local level.

Eligible patients aged 40–80 years must have a confident clinical and radiographic*/ or histological* diagnosis of IPF according to 2011 IPF guidelines (ATS 2011). Patients with possible UIP on high-resolution computed tomography and without SLB in case of "working diagnose" of IPF during multidisciplinary team (MDT) discussion, are also eligible for the trial (see Table 2).

Patients will be required to have a relative %FVC ≥ 40 %, percent predicted carbon monoxide diffusing capacity (%DL_{CO}) ≥ 30 %, and able to walk ≥ 100 meters during the 6-minute walk test at the Screening.

All assessments in the study will be initiated only after signed Informed Consent is obtained from the patient. For this purpose, an additional visit may be perfomed prior to the start of the Screening procedures and an appropriate review of the patient's clinical data relevant to the IPF diagnosis is done (see Appendix 1).

Any patient identified for the study must discontinue all prohibited therapies including therapy targeted to treat IPF for at least 28 days before the start of the treatment period. Other than permanent use of corticosteroids (prednisolone at a maximum daily dose of 15 mg or equivalents) and brief periods of corticosteroid use for acute IPF exacerbation, patients will not receive any other therapy for the treatment of IPF (see Section 4.4). After central review of HRCT and SLB, patients will enter the Screening period, which may last up to 28 days (4 weeks).

After the Screening, eligible patients will enter the Treatment period lasting 26 *(± 1)* weeks. All patients will receive pirfenidone 2403 mg/d administered orally in divided doses three times per day (TID) with food. Dose of the study treatment will be titrated

over 14 days to the full dose of 9 capsules per day (three 267 mg capsules taken orally TID with food). Patients will remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced to manage adverse events or titrated again when restarting study treatment after an appropriate interruption in treatment (see Section 5.1.2).

The primary efficacy endpoint in the study is the change from baseline to Week 26 in absolute (mL) FVC and relative (%) FVC as measured by spirometry procedure. Spirometry will be performed at the Screening, on Day 1 of treatment, at Week 12, Week 26 and in the extended Follow-up period (Weeks 39 and 52), if applicable. At screening, spirometry measurements will be performed before and after administration of albuterol (or salbutamol) from a metered dose inhaler. During further visits, bronchodilator test is not necessary to perform. Spirometry data collected throughout the study will be evaluated by local readers.

Patients will have a telephone assessment at Week 1, when safety-related information and adherence to treatment is collected. Subsequently patients will have in-clinic visits at Weeks 2, 4, 8, 12, 16, 20 and 26. Patients should complete an adverse event and dosing compliance diary between all visits. Additionally, telephone calls to patients will be scheduled at Weeks 3, 5, 7, 13 and 24 as a part of IPF care program. A total of 5-7 calls are scheduled in the study, including extra-calls at Weeks 8 and 10 as needed.

Treatment with pirfenidone will continue until Week 26 *(± 1).* Patients will be followed through the Follow-up visit scheduled 2-4 weeks after treatment completion or until entry into the long-term follow-up (rollover study), whichever occurs earlier. Patients who undergo lung transplantation or who chose to withdraw from study procedures early will be followed for vital status until Week 26. If patients discontinue study treatment early for any reason, they should continue with all scheduled study procedures through Week 26.

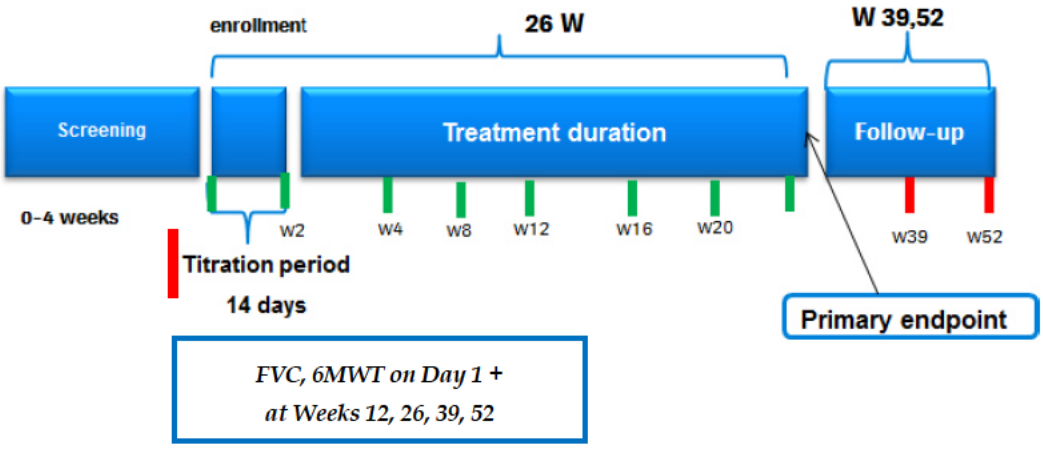
Patients who complete participation in the study prematurely due to any reasons (drop-outs) will not be replaced.

Patients who proceed until Week 26 in the study and are compliant with the study treatment, may continue treatment with commercially available pirfenidone after study completion in real clinical practice (long-term follow-up or rollover study). In this case, patients will have two follow-up assessments of FVC and 6MWT at Weeks 39 and 52 and CT scans evaluation at Week 52. Information on AEs occurance will also be collected during the rollover part of the study.

If a patient cannot participate in the rollover part of the study for any reason, a follow-up visit will be performed 14-28 days after the last dose of pirfenidone is taken.

The study schema is presented in Figure 1 below. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



An Independent Data Monitoring Committee (IDMC) will be implemented in the study. The IDMC will conduct regular review of the trial safety data, with the focus on death cases, serious adverse events, unexpected adverse events, adverse events leading to treatment or study discontinuation, liver enzyme increases, reported as adverse events, and other AEs immediately reported to the Sponsor (see *Section 5.2.3.2*).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or long-term follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur after 12 months after the last patient is enrolled.

The total length of the study, from recruiting of the first patient to the end of the study, is expected to be approximately 2 years. Duration of participation in the study for an individual patient is between *31* and *35* weeks (excluding long-term follow-up). For patients continuing in the rollover study the duration of participation in the study extends up to *maximum 58* weeks.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Pirfenidone Dose and Schedule

Posology and schedule of administration, including dose titration, of pirfenidone in the current study are *those* recommended *in the official Russian instruction for use of the IMP.*

These dose and schedule of administration of pirfenidone were evaluated in previous controlled clinical trials (CAPACITY-004, -006, ASCEND), which demonstrated favorable efficacy and safety results compared with placebo.

3.3.2 Rationale for Patient Population

Based on results from the previous studies, the eligibility criteria have been modified/ broadened (including a confident and "working" diagnosis of IPF, patients with %FVC ≥ 40% and $\%DL_{CO}$ ≥ 30%) to ensure that appropriate population will be enrolled to more closely correspond to real clinical practice in Russia. This would support estimating findings, which were observed in previously conducted studies of pirfenidone. It is expected, that studied population diagnosed IPF with mild to moderate deterioration of lung function would benefit from the treatment with pirfenidone.

3.3.3 Rationale for Control Group

The study is non-controlled by design. The choice of the non-controlled design is supported by the following positions:

- Enrolment of patients with rare disease in a clinical study is challenging and presumes ethical issues to be addressed in the design. Pirfenidone has been granted an orphan designation in Europe and the USA. Idiopathic pulmonary fibrosis is listed in the Russian Ministry of Healthcare registry of rare (orphan) diseases, so pirfenidone *obtained* the status of an orphan drug in Russia, too.

- Efficacy of pirfenidone has been previously demonstrated in a number of placebo-controlled studies and meta-analyses, therefore, additional placebo-controlled study in patients with poor prognosis is deemed unethical.

- There is no adequate literature data to design a comparative active-controlled study of pirfenidone; non-inferiority study is merely feasible.

Taking into consideration all the mentioned above, non-controlled design is considered acceptable for the current study from the regulatory and ethical positions.

3.3.4 Rationale for Open-Label Design

Open-label design is chosen resulting from the absence of the control group.

3.3.5 Rationale for Endpoint Selection

Primary endpoint rationale

Decline of FVC over 6 months was convincingly shown to be associated with overall prognosis in patients with IPF. Pathophysiologically, fibrotic remodelling of the lung interstitium, with a subsequent restrictive ventilatory defect represents the core element of the histopathology of IPF. Consequently, any intervention which can slow the fibrosis leading to lung restriction is expected to be determined by a reduction in FVC decline. This reduction has the potential to ultimately improve prognosis in IPF.

The primary endpoint of the study, change in FVC from baseline to Week 26, represents a clinically meaningful outcome measure that has been demonstrated to be reliable, valid, and predictive of changes in other important clinical endpoints in patients with IPF (du Bois et al. 2009). Many researchers reported previously that a decrement in %FVC over 6 months, particularly if ≥ 10% in magnitude, is both clinically significant and highly predictive of mortality (Collard et al. 2007; Flaherty et al. 2003; Zappala et al. 2010). Therefore, 6 months' timeframe for the assessment of the primary outcome is sufficient to estimate treatment effect.

Secondary endpoints rationale

In addition to a poor prognosis for life expectancy, patients with IPF suffer from dyspnea and decrease of tolerability to physical activity. This substantially reduces the quality of life and cause major restriction in everyday activity and incapacity in many patients with IPF. It is therefore considered valuable to estimate potential influence of the study treatment on patient-reported outcomes (Borg scale, EQ-5D).

Exploratory endpoints rationale

The 2011 IPF guidelines provide updated and simplified IPF diagnostic criteria proposed by the ATS/ERS/JRS/ALAT, which may result in HRCT scanning playing a central role in the diagnosis of IPF. Technological advances in HRCT have brought an opportunity of HRCT as an accurate, sensitive and objective technique for evaluating IPF.

In addition, physicians often observe patients who exhibit worsening of HRCT findings associated with a poor prognosis in clinical practice. Additional exploratory objective of

this study is to assess the changes in HRCT findings using a new HRCT scoring system based on the grading scale.

Evaluation of the number of exacerbations is a clinically significant outcome but can only serve as an exploratory additional outcome, due to the low frequency of such events, and low number of patients in the trial.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study population consists of approximately 60 male and female patients with IPF diagnosis aged 40–80 years. Eligible patients must meet the inclusion and exclusion criteria outlined below.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Male and female patients aged 40–80 years, inclusive.

2. Clinical symptoms consistent with IPF of ≥ 6 months duration.

3. Patients should have both “confident” or “consistent” with UIP diagnosis of IPF based on clinical, radiologic or pathologic data according to 2011 ATS/ERS guidelines at the Screening. HRCT scan performed within 24 months before the start of the Screening may be used.

4. No features supporting an alternative diagnosis on transbronchial biopsy, bronchoalveolar lavage (BAL), or surgical lung biopsy, if performed. Results of the surgical lung biopsy performed within the last 4 years must be confirmed by central review.

5. Patients with %FVC ≥ 40 % at the Screening.

6. Patients with $\%DL_{CO}$ ≥ 30 % at the Screening.

7. Ability to walk ≥ 100 m during the 6-minute walk test at the Screening.

8. Eligible patients must discontinue all prohibited medications at least 28 days before the *start of treatment*.

9. Female patients of childbearing potential must have negative urine pregnancy test at the Screening and before first dosing on Day 1.

10. Patients able to conceive must agree to use safe contraceptive methods for the whole duration of the study and 28 days after the last dosing.

    a. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 28 days after the last dose of pirfenidone. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of highly effective contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUD), and copper intrauterine devices.

    b. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

       With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of pirfenidone to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

       The reliability of sexual abstinence of patients of both sexes should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

11. Ability to understand and sign Informed Consent Form.

12. Ability to comply with the study protocol, in the investigator's judgment (e.g. ability to fill out patient diary and other patient-reported outcome tools).

13. Able to understand the importance of adherence to study treatment and the study protocol and willing to follow all study requirements.

4.1.2 Exclusion Criteria

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

Disease-Related Exclusions:

1. Significant clinical worsening of IPF between Screening and Day 1, in the opinion of the investigator.

2. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC < 0.7) *at the Screening*.

3. In the opinion of the investigator patients with predicted life expectancy <12 months or those who are on an active transplant waiting list.

4. Cigarette smoking within 28 days before the start of treatment or unwilling to avoid tobacco products throughout the study.

5. History of clinically significant environmental exposure known to cause pulmonary fibrosis (PF), including but not limited to drugs (such as amiodarone), asbestos, beryllium, radiation, and domestic birds.

6. Known explanation for interstitial lung disease, including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis, and cancer.

7. Clinical diagnosis of any connective tissue disease, including but not limited to scleroderma, polymyositis/ dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis, *or patients with positive biomarker tests associated with these diseases (rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibodies) at the Screening*.

8. During baseline analysis of HRCT, significant coexistent emphysema (emphysema extent greater than extent of fibrosis) confirmed by central review.

9. Planned lung transplantation during the study.

10. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis.

Medical Exclusions:

11. Unable to perform 6MWT or to undergo pulmonary function test.

12. Any history of malignancy likely to result in significant disability or likely to require significant medical or surgical intervention within the next 1 years. This

does not include minor surgical procedures for localized cancer (e.g., basal cell carcinoma).

13. History of severe hepatic impairment or end-stage liver disease.

14. History of end-stage renal disease requiring dialysis.

15. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous 6 months, including but not limited to the following:

    a. unstable angina pectoris or myocardial infarction

    b. congestive heart failure requiring hospitalization

    c. uncontrolled clinically significant arrhythmias

16. Pregnancy or lactation, or intention to become pregnant during the study. Women of childbearing capacity are required to have a negative urine pregnancy test before treatment and must agree to maintain highly effective contraception.

17. History of alcohol or substance abuse in the past 1 year.

18. History of gastrointestinal (GI) tract perforation or history of peptic ulcer within six months.

19. Family or personal history of long QT Syndrome.

20. Known hypersensitivity to pirfenidone during prior treatment or any excipient of the study treatment.

21. Use of any of the following therapies within 28 days before the start of treatment period:

    a. investigational therapy, defined as any drug that has not been approved for marketing for any indication in Russia

    b. any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, tumor necrosis factor (TNF)-α

inhibitors, N-acetylcysteine (NAC), imatinib mesylate, interferon gamma-1b (IFN γ-1b), and tyrosine kinase inhibitors

c. medications that are specifically used for the treatment of IPF including but not limited to angiotensin converting enzyme (ACE) inhibitors, colchicine, corticosteroids (prednisolone at doses exceeding 15 mg/day or equivalents), heparin, warfarin, and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication

d. fluvoxamine

e. sildenafil (chronic use for pulmonary arterial hypertension). Note: intermittent use for erectile dysfunction is allowed.

Laboratory Exclusions:

22. Any of the following liver function test outside specified limits at the Screening:

    a. total bilirubin above the upper limit of normal (ULN);

    b. aspartate or alanine aminotransferase (AST or ALT) > 3 × ULN;

    c. alkaline phosphatase > 2.5 × ULN.

23. Creatinine clearance < 30 mL/min, calculated using the Cockcroft-Gault formula (see *Section 4.5.8*).

24. Electrocardiogram (ECG) with a QT interval corrected according to Fridericia's formula (QTcF) > 500 msec at the Screening.

Other Exclusions:

25. Inability to return for follow-up visits or obtain follow-up data required to assess study therapy, or presence of other reasons for anticipated non-compliance to therapy or procedures, in the opinion of the investigator.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The study is a single-arm, open-label by design. All patients will receive pirfenidone 2403 mg/d orally in divided doses TID after titration period of 14 days (Section 4.3.2).

Therefore, treatment allocation methods and blinding/ unblinding procedures are not applicable in the study.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is Pirfenidone (trade name Esbriet, drug code RO0220912) (INN: pirfenidone, ATC code L04AX05) 267 mg capsules, manufactured by Catalent Pharma Solutions, Winchester, USA.

The terms "study drug" and "study treatment" are used throughout the protocol and refer to the test product pirfenidone.

4.3.1 Formulation, Packaging, and Handling

Pirfenidone will be supplied to the study sites by the Sponsor (F. Hoffmann-La Roche Ltd., Switzerland) as needed.

Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear labeling with identification required by law, the protocol number, drug identification, and dosage. The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

Formulation

Pharmaceutical form: hard capsules (capsules).

Composition: each capsule contains: active substance - 267 mg pirfenidone (82.15%); excipients - croscarmellose sodium 8.15%, microcrystalline cellulose 7.39%, povidone, USP, EP 1.85%, magnesium stearate 0.46%.

Appearance: two piece hard capsules with a white to off-white opaque body and white to off-white opaque cap imprinted with “PFD 267 mg” in brown ink and containing a white to pale yellow powder.

Packaging and labelling

Study treatment will be supplied in bottles, 270 capsules per bottle.

Bottles will be labeled for investigational use only according to applicable regulations of the Russian Federation.

Storage

Investigator is responsible for appropriate storage of the study drug. Investigator should maintain temperature in the room of storage and fill out temperature log on regular basis. *The study drug must be stored as prescribed in the official Russian instruction for use of pirfenidone (Esbriet). Shelf life is indicated on label. Study drug must not be used beyond the expiration date.*

Handling

Study treatment will be dispensed by the responsible investigator or investigational site pharmacist only to the participants of this clinical study. Drug accountability must be confirmed in written by the responsible employee of the site (see Section 4.3.3). Detailed Instructions for handling of the study drug will be provided to investigational sites as appropriate.

4.3.2 Dosage, Administration, and Compliance

Study treatment will be initiated on Day 1 in patients who completed Screening period successfully and fully comply for the study. *Study treatment will continue until visit at Week 26 (± 1 week), unless terminated earlier for reasons indicated in Section 4.6.2, or patient is proceeding in the rollover study.*Pirfenidone will be taken orally in a daily dose of 2403 mg in divided doses three times per day with food. Study treatment should be titrated over 14 days, as tolerated, to the full dose of 9 capsules per day (three capsules TID), as follows:

- Days 1 to 7: one capsule TID (801 mg/day)
- Days 8 to 14: two capsules TID (1602 mg/day)
- Day 15 and continuing: three capsules TID (maximum of 9 capsules daily equal to 2403 mg/day).

Each dose should be taken with food, with a drink of water, at the same time each day. Patients will remain on a stable maintenance dose for the duration of the study period unless the dose is reduced to manage AEs. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Any overdose or incorrect administration of the study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events

associated with an overdose or incorrect administration of the study drug should be recorded on the Adverse Event eCRF. *Section 5.3.5.10* summarizes available safety data related to overdosing of pirfenidone.

4.3.3 Investigational Medicinal Product Accountability

IMP required for completion of this study will be provided by the Sponsor as required by the local health authority regulations. The study site will acknowledge receipt of the IMP, using the Interactive Web Response System (IWRS) for Patient Randomization and Trial Supply Management or by returning the appropriate documentation form, to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

Study treatment will be dispensed to the patient every 12 weeks, but may be dispensed at other visits, as needed. Patients will be instructed to store study treatment at room temperature. Patients will be instructed to use study treatments as prescribed by the investigator and to keep and return to the investigator all used and unused bottles of the study *drug upon completion of the study treatment*.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log. After drug accountability has been verified, sites will return all used and unused study treatment bottles to the Sponsor in accordance with applicable standard operating procedures.

4.3.4 Post-Trial Access to Pirfenidone

Roche is committed to a high standard of quality and ethical conduct in all aspects of conducting clinical trials. As part of this commitment and in accordance with the Declaration of Helsinki, Roche offers patients who participate in Roche-sponsored clinical trials continued access to IMP. However, in this trial Roche is not obliged to provide pirfenidone to patients who have completed the 26-week study, due to the fact that investigational medicinal product will be commercially marketed in Russia and reasonably accessible to the patient. Also, there is availability of appropriate alternative treatment to the patient on Russian market.

The patients can continue treatment with pirfenidone in routine clinical practice according to the local label.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Collection of concomitant medication data is ceased if a patient enters the rollover study.

4.4.1 Permitted Therapy

Corticosteroids may be used permanently at the discretion of the investigator as a part of routine management of IPF (at a maximum daily dose of 15 mg of prednisolone or equivalents). Corticosteroids may also be used without dose restriction for a period of up to 21 days in patients experiencing an episode of acute IPF exacerbation. The study drug should be continued during exacerbations, if possible. If study treatment interruption or discontinuation is considered, it must be immediately reported by telephone to Sponsor's Medical Monitor or designee.

An acute IPF exacerbation is defined in updated publication (Collard HR et al., *2016)*.

The diagnostic criteria:

- Previous or concurrent diagnosis of IPF;
- Acute worsening or development of dyspnea typically <1 mo duration;
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern;
- Deterioration not fully explained by cardiac failure or fluid overload.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 28 days prior the start of treatment period:

- investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site;
- corticosteroids at a daily doses exceeding 15 mg/ day of prednisolone or equivalents when used for the treatment of IPF (except for durations of up to 21 days for acute IPF exacerbation, see Section 4.4.1). No restrictions apply to corticosteroids used for reasons other than IPF therapy (e.g., allergic reactions, sepsis); however, the specific reason for use must be recorded;
- cytotoxic, immunosuppressive, cytokine-modulating, or receptor antagonist agents including, but not limited to, azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, D-penicillamine, colchicines, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, TNF-α inhibitors, NAC, IFN-γ1b, and tyrosine kinase inhibitors;
- concomitant medications used for the treatment of IPF including but not limited to ACE inhibitors, warfarin, heparin, and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication, if there is no clinically acceptable alternative therapy for the same indication; however, the specific reason for use must be recorded;
- sildenafil (daily use). Note: intermittent use for erectile dysfunction is allowed.

In vitro data suggest that pirfenidone is metabolized by CYP1A2 without apparent inhibitory activity on the enzyme, however, there is a potential for drug-drug interaction with any medication that is metabolized by or strongly inhibits or induces this enzyme. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with pirfenidone:

- strong CYP1A2 inhibitors, including, but not limited to, fluvoxamine and enoxacin (a 2- to 4-fold increase in exposure to pirfenidone);
- moderate CYP1A2 inhibitors, including, but not limited to, ciprofloxacin, amiodarone, propafenone.

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

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

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

4.4.3 Prohibited Food

Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with pirfenidone.

No special diet or dietary restrictions are otherwise designated in the study, unless recommended by the investigator for the treatment of adverse events.

4.4.4 Additional Restrictions

Patients should stop smoking at entering the treatment period (not less than 28 days before the start of treatment) as smoking is known to induce metabolism of the study drug and thus attenuate treatment effect. Smoking patients will not be enrolled in the study.

All participants will be warned of the potential photosensitivity skin adverse reactions and will be advised to use sunscreens during exposure to direct sunlight.

4.5 STUDY ASSESSMENTS

Study procedures are defined as laboratory tests, spirometry, DL_{CO} measurement, ECG, HRCT scan, directed medical history, physical examination, vital signs, height, weight, GAP risk assessment, 6MWT and Borg Scale, EQ-5D questionnaire, procedures for eliciting AEs and any changes to existing treatment regimens.

Patients will be followed through the Follow-up visit scheduled 2-4 weeks after treatment completion on Week 26 *(± 1)* or until entry into the long-term follow-up (rollover study), whichever occurs earlier. Patients who undergo lung transplantation or who choose to withdraw from study procedures early will be followed for vital status until Week 26.

Please see Appendix 1 for the schedule of activities to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

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

An additional Informed Consent visit may be perfomed prior to the start of the Screening procedures and an appropriate review of the patient's clinical data relevant to the IPF diagnosis is done (see Appendix 1).

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria within 4 weeks before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

All patients should be notified of the necessity to use safe contraceptive methods during participation in the study and 28 days after its completion or discontinuation (see Section 4.1.1).

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to treatment period will be recorded.

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

4.5.3 Physical Examinations

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

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

4.5.4 Weight and Height

Weight and height will be measured as outlined in Appendix 1. Height will be assessed at the Screening only.

4.5.5 Vital Signs

Vital signs will be measured by the investigator at the Screening and subsequent visits and include measurements of respiratory rate (breaths/ minute), pulse rate (beats/ minute), and systolic and diastolic blood pressure (mmHg), and axillary temperature (ºC).

Respiratory rate will be measured in patient's resting position by counting chest movements per minute. Blood pressure and pulse rate will be measured in the supine/ sitting position. All recordings should be made using the same blood pressure recording instrument. Pulse rate is defined as radial pulse counted for 30 seconds in the supine/ sitting position. Body temperature is defined as axillary temperature (ºC).

4.5.6 HRCT and Surgical Lung Biopsy

4.5.6.1 High-Resolution Computed Tomography

HRCT scans should be obtained before the Screening period as part of the routine practice for a patient. It may be used to confirm eligibility. For eligibility confirmation acceptable HRCT scans should be dated not earlier than 2 years before the Screening.

Baseline HRCT scans will be performed only in those patients who have no acceptable scans within 2 months before the start of treatment period (Day 1) and had no IPF exacerbations within this period. Semiquantitative analysis of CT scans with HRCT fibrosis score calculation should be performed in each timepoint as outlined in the schedule of study assessments (see Appendix 1).

All HRCT images are to be read by the site's local radiologist reader at first. Additionally, for eligibility confirmation the HRCT scans will be reviewed by two central readers who are radiologists with expertise in IPF. If the first expert (central reader-1) agrees with the local opinion, the second expert (central reader-2) will not review scans. If the first expert disagrees with the local opinion, the second expert should review scans.

HRCT acquisition in the study will be performed using the same scanning protocol. Images in a particular site should be read by the same local specialist. Further semiquantitative assessments of CT scans for fibrosis scores will be performed by one central reader. Detailed HRCT acquisition protocol and fibrosis scoring system are described in Appendix 2.

All HRCT digital scans should be stored on a dedicated disk or tape at each study center. The images will be transferred electronically to the central readers responsible for interpretation of the images.

Data regarding the HRCT interpretation will be entered electronically into the vendor's database and incorporated into the clinical database.

4.5.6.2 Surgical Lung Biopsy

Histopathological assessment of the lung tissue samples obtained within 4 years before the Screening should be performed centrally for eligibility confirmation. Histopathological evaluation, if not available, is not repeated at the Screening.

Transbroncheal biopsy or BAL are not mandatory and will only be reviewed at the Screening, if available, to exclude other causes of PF.

Histopathologic criteria for UIP are outlined in Appendix 3. Samples will be submitted and reviewed by one of the two central readers who are pathologists with expertise in IPF. Data regarding the pathology findings will be entered directly into the electronic case report form (eCRF).

The observations of the central readers in radiology and pathology will be stored in the clinical database. Based on the algorithm detailed in Table 2, patient eligibility will be communicated to the study site by the Sponsor's designated vendor.

Table 2 Summary of Select Criteria for Diagnosis of IPF

	Surgical Lung Biopsy Not Available	**Pathology Panel: Definite UIP**	**Pathology Panel: Probable UIP**	**Pathology Panel: Possible UIP**	**Pathology Panel: Inconsistent with UIP or Not Classifiable**
Radiology Panel: Definite UIP	Eligible	Eligible	Eligible	Eligible	NOT Eligible
Radiology Panel: Possible UIP	Eligible	Eligible	Eligible	NOT Eligible	NOT Eligible
Radiology Panel: Inconsistent with IPF	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

4.5.7 Spirometry and DL_{CO} Measurements

Spirometry and PFT will be standardized and performed as described in ATS recommendations (ATS 2005).

FVC

FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, i.e. vital capacity performed with a maximally forced expiratory effort, expressed in litres at body temperature and ambient pressure saturated with water vapour (ATS 2005).

At screening, spirometry measurements of FVC will be performed before and after administration of albuterol (or salbutamol) from a metered dose inhaler. Four separate doses of 100 mg should be used when given by metered dose inhaler using a spacer. Tests should be repeated after a 15-min delay. *During further visits, bronchodilator test is not necessary to perform.*

DL_{CO}

DL_{CO} will be measured by determining the diffusing capacity of the lung for carbon monoxide corrected to hemoglobin. DL_{CO} measurement should be performed before or at least 30 min after the last bronchodilator puff*, in case bronchodilator test has been*

performed. It is measured by a single breath technique where helium and carbon monoxide are rapidly inspired, held for several seconds and then expired with the measurement of the remaining carbon monoxide. Comparison of the inspired and expired CO fractions allows calculation of DL_{CO} (Ranu et al. 2011).

Results of DL_{CO} measurements should be corrected to patients' hemoglobin (Hb) using one of the formulas (Cotes et al. 1979):

Hb-corrected DL_{CO} for men: $DL_{CO} \times (10.22 + Hb)/(1.7 \times Hb)$

Hb-corrected DL_{CO} for women: $DL_{CO} \times (9.38 + Hb)/(1.7 \times Hb)$

where Hb indicates the value of hemoglobin, in g/dL. If the Hb value is reported in g/L, then the Hb value is divided by 10. If the Hb value is reported in mmol/L, then the Hb value is divided by 0.6206.

Use the hemoglobin value available on the same day if possible; otherwise, the closest hemoglobin value before or after the actual DL_{CO} assessment date should be used. If the two values are equidistant, the value before the actual DL_{CO} assessment should be used (Cotes et al. 1979).

Lung fuction assessments in one patient during the study should be performed using the same equipment and by the same investigator. All spirometry and DL_{CO} data collected throughout the study will be evaluated by local readers. Data for FVC and DL_{CO} will be entered by the study staff into the eCRF electronically.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

All samples for laboratory tests (hematology, blood chemistry, serologic tests) will be analyzed in the study site's local laboratory.

Blood samples should be obtained in fasted patients and handled appropriately. The following parameters will be utilized in the study:

- hematology (plasma): white blood cells (WBC) count, red blood cells (RBC) count, hemoglobin, hematocrit, platelet count, (relative) differential WBC count (neutrophils, eosinophils, basophils, monocytes, lymphocytes);

- blood chemistry panel (serum or plasma): albumin, alkaline phosphatase (AP), ALT, AST, direct bilirubin, total bilirubin, total protein, albumin, cholesterol, creatine kinase (CK), creatinine, triglycerides, gamma-glutamyl transferase

(GGT), glucose, lactic dehydrogenase (LDH), calcium, phosphorus, magnesium, potassium, sodium, urea nitrogen, uric acid;

- serologic tests (at screening only, exclusion tests): rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibody titer.

Creatinine clearance

Creatinine clearance should be assessed at the Screening for eligibility confirmation using the following formula by Cockcroft-Gault (Cockcroft DW et al, 1976):

For serum creatinine concentration in mg/dL:

$$CrCl\ (mL/min) = (140 - age\ (years)) \times weight\ (kg) \times 1.0 / 72 \times serum\ creatinine\ (mg/dL)$$

For serum creatinine concentration in µmol/L:

$$CrCl\ (mL/min) = (140 - age\ (years)) \times weight\ (kg) \times 1.0 / 0.81 \times serum\ creatinine\ (\mu mol/L)$$

Pregnancy test

All women of childbearing potential will have a urine pregnancy test at the Screening and on Day 1 before start of treatment. Only women with negative pregnancy test will be included in the study. Urine pregnancy tests will be performed repeatedly at specified subsequent visits as scheduled in the Appendix 1.

If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Women with confirmed positive pregnancy test should be immediately withdrawn from the study treatment (see Section 5.4.3). Urine pregnancy test will be performed by the investigator using test-strips with least sensitivity to human chorionic gonadotropin (hCG) of 10 mLU/mL.

The investigator can perform clinical laboratory assessments more frequently, if it is clinically indicated.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Biological samples will be destroyed immediately after analyzing.

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 will be subject to the confidentiality standards described in Section 8.4.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws*, bronchodilator test*) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper and digital copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected for heart rate using Fridericia's method (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the QTcF is $>$ 500 ms and/ or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes or in the utmost 24 hours, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. A decision on study drug discontinuation should be made, as described in Section 5.1.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.10 6-Minute Walk Test

The 6MWT measures the distance *in meters* that a patient can walk at his/her own pace on a measured, flat hard surface in a period of 6 min. The 6MWT assesses the global and integrated responses of all body systems involved during walking. The 6MWT based

on ATS recommendations (ATS 2002) will be performed as outlined in the Reference Guide.

4.5.11 Patient-Reported *and Clinician-Reported* Outcomes

PRO data will be collected via questionnaires to document the treatment benefit of pirfenidone. ClinRO data will be collected using a scale for patient clinical assessment at baseline. The validated scales and questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

4.5.11.1 Borg Scale

The Borg Scale is an instrument to be self-administered by the patient as part of the 6MWT procedure (Borg 1982) (see Appendix 4). The Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, the patient should tick the answer to the question: *"Please rate the current severity of your breathlessness by circling the most appropriate number on the following scale."* At the end of the exercise, the patient should grade his breathing level again.

Study staff will enter the 6MWT data into the eCRF.

4.5.11.2 EuroQol 5-Dimension Questionnaire

The European Quality of Life (EuroQol) 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group, 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; Jindal et al. 2011; Behr J et al. 2013).

There are two components to the EuroQol EQ-5D: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D will be utilized in this study for economic modeling.

*EQ-5D-5L questionnaire (Self-completed version on paper 1.0) will be used in the study. A sample of the validated questionnaire in English (for UK) is provided in Appendix 5. A validated version (Self-completed version on paper 1.0) in a local (Russian) language will be given to the patients for completion.*The questionnaire will be administered on the visits as outlined in the schedule of activities (see Appendix 1) and prior to any interventions. The patients will be provided with a hard copy of a questionnaire and a pen. Patients should be given ample time for questionnaire completion.

4.5.11.3 GAP Risk Assessment System

The GAP (Gender, Age, Physiology) risk assessment system is a validated clinical prediction tool for estimating prognosis in patients with IPF. It consists of two complimentary prognostic tools intended to inform, but not replace clinical judgment.

First, the GAP index and staging system provides a simple screening method for determining the average risk of mortality of patients by GAP stage. Second, the GAP calculator provides an estimation of individual risk of mortality for those patients in whom a more precise estimation of risk may further inform patient care (see Appendix 6).

The GAP risk assessment system is utilized at baseline only. Points for each variable of the scoring system will be entered by the investigator directly into the eCRF. GAP index and an estimation of individual risk of mortality will be calculated automatically by the system (Ley et al. 2012).

GAP risk assessment is utilized on the basis of predicted DL_{CO} values. The formulas for computing predicted DL_{CO} are as follows (Crapo and Morris 1971):

Predicted DL_{CO} for men 0.410 × height (cm) − 0.210 × age (yr) − 26.31

Predicted DL_{CO} for women 0.282 × height (cm) − 0.157 × age (yr) − 10.89.

4.5.12 IPF Care Program

IPF Care Program is a program developed by the Sponsor to support patients with the debilitating lung disease, who are enrolled in the study. The program is implemented to improve patients' compliance to the study treatment and reduce number of drop-outs. The program consists of telephone calls to the patient scheduled at specific timepoints and voluntary information materials for patients.

Telephone calls

Telephone calls to patients will be scheduled at Weeks 3, 5, 7, 13 and 24. Additional calls can be performed at Weeks 8 and 10 as needed. A total of 5-7 calls are scheduled in the study. Topics for discussion will include the following:

- Explanation of the IPF disease nature
- Pirfenidone titration and dosing
- Management of side effects
- Everyday life
- Answering questions
- Necessity of additional calls.

A detailed schedule of calls and topics for discussion at each timepoint is presented in Appendix 7.

Investigator should record in the eCRF the date and time of the IPF Care Program calls.

Information materials

The following materials will also be provided to all patients participating in the trial:

- Patient information brochure (information on treatment with pirfenidone)
- Pocket guide (brief information on treatment with pirfenidone)

The materials will be supplied by the Sponsor and dispensed by the investigators or other designated staff. Samples of the IPF Care Program will be provided to the study sites as separate documents.

4.5.13 *Details on* the Study Visits

Before starting any study specific procedures, investigator must have HRCT and surgical biopsy (if applicable) performed in routine practice *confirming diagnose of IPF* to assess eligibility of patient..

4.5.13.1 Informed Consent Visit

Written informed consent must be obtained before initiating any study-associated procedures or changes to a pre-existing treatment regimen for purposes of this study. Informed Consent Visit *is* performed for explaining the study, collecting Informed Consent, handing out the Patient Information, collecting and sending HRCT or surgical biopsy (if applicable) and also for starting the washout medication prior 28 days to start of treatment. Any patient *identified* for the study, must discontinue all prohibited medications and stop smoking at least 28 days before *the* start of treatment. This is the Washout Period. If a medication must be tapered, tapering must start early enough that the patient has discontinued the drug 28 days before the start of treatment. Written informed consent must be obtained before withdrawing or tapering the patient off prohibited therapies.

After signing *the* Informed consent, the investigator must review and transfer for central review HRCT scans, surgical lung biopsies (if available), which were performed in routine practice, to assess eligibility. (HRCT must be no older than 24 months. Results of the surgical lung biopsy must be no older than 4 years).

The investigator must explain to the patient that entry into the study is not guaranteed.

4.5.13.2 Screening Period (Day -28 to Day -1)

Procedures conducted during Screening will be used to determine the eligibility of each patient for study enrollment before initiation of treatment and to establish patient baseline status. If patients fail Screening due to a condition that subsequently resolves (e.g., infection), they may be considered for rescreening; however, these patients must be discussed with the study *M*edical *M*onitor or designee before rescreening. *In case of rescreening, the patient must be reconsented.*

The Screening period is defined as the time between the date of the first Screening procedure and Day -1 and may last up to *28* days. Screening procedures may be conducted on different days within the Screening period, if convenient. The order of procedures is not strict; however, basic requirements to be followed are given in gaps below.

The following procedures will be performed during Screening:

- Demographic data
- Review and update medical history and concomitant medications
- EQ5D questionnaire (should be performed before any other non-PRO assessments)

- *ECGs (obtained before bronchodilator administration or on a separate day) All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, weight, and height
- Clinical laboratory assessments, including hematology, serum chemistries, serologic tests, and pregnancy test for women of childbearing capacity (blood samples must be drawn in fasted state)
- HRCT scan for baseline assessment (for patients with HRCT scans performed more than 2 months before the treatment period or with scans not meeting the imaging acquisition criteria outlined in Appendix 2)
- *Review transbronchial lung biopsy/ BAL;*
- Spirometry (FVC) (before and after bronchodilator administration with a 15 min delay).Collection and recording of the retrospective FVC values obtained in clinical practice over the last year.
- 6MWT and Borg Scale
- DL_{CO} (obtained before or 30 min after bronchodilator administration)
- GAP assessment
- Eliciting AEs

4.5.13.3 Start of Treatment (Day 1)

Treatment must be initiated no more than *28* days after the start of screening. All Day 1 procedures must be performed before administration of the study treatment. This study has no Day 0.

The following procedures will be performed on Day 1:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECGs. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight

- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity (blood samples must be taken in fasted state)
- Spirometry (FVC)
- 6MWT and Borg Scale
- Confirmation of patient eligibility for study participation
- Instruct the patient on how to titrate the dose of study treatment
- Dispense 12-week supply of study treatment. Dosing should start on the Day 1
- Dispense patient diary and instruct patients on how to properly record information using the diary.

4.5.13.4 Week 1 Telephone Assessment (± 1 Day)

A telephone interview will be conducted to determine vital status and to assess tolerability of study treatment, patient compliance with dosing, and titration of study treatment.

4.5.13.5 Weeks 2, 4, and 8 (± 2 Days)

The following procedures will be performed at Weeks 2, 4, and 8:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- *ECG (at Weeks 4 and 8 only)/ All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity (pregnancy test at Weeks 4 and 8 only)
- Review patient's diary

4.5.13.6 Weeks 12 (± 2 Days)

The following procedures will be performed at Week 12:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)

- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, and pregnancy test for women of childbearing capacity
- Spirometry (FVC)
- 6MWT and Borg Scale
- Review patient's diary

4.5.13.7 Weeks 16 and 20 (± 1 Week)

The following will be performed at Weeks 16 and 20:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing)
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity (pregnancy test at Week 20 only)
- Review and dispense new diary, if required.

4.5.13.8 Week 26 (± 1 Week)

The following will be performed at Week 26 (on two separate days):

1st day at Week 26:

- Physical examination, vital signs
- Spirometry (FVC)
- 6MWT and Borg Scale

2nd day at Week 26:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations)
- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECG. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs, and weight
- Clinical laboratory assessments, including hematology, serum chemistries, pregnancy test for women of childbearing capacity

- HRCT
- Spirometry (FVC) 6MWT and Borg Scale
- Collect patient's diary

4.5.13.9 Follow-up Visit (14-28 Days after Last Dosing)

The following will be performed at follow-up:

- Directed history (including review of AEs/SAEs, concomitant medications, oxygen use, and hospitalizations)
- Physical examination, vital signs, and weight
- Clinical laboratory assessments (hematology, serum chemistries)
- Estimating patient's further participation in the rollover study

4.5.13.10 Long-Term Follow-Up/ Rollover Study

Week 39 (± 2 weeks)

The following will be performed at Week 39:

- Physical examination, vital signs
- Clinical laboratory assessments (hematology, serum chemistries)
- Spirometry (FVC)
- 6MWT and Borg Scale
- Review AEs

Week 52 (± 2 weeks)

The following will be performed at Week 52:

- EQ5D questionnaire (should be performed before any other non-PRO assessments)
- *ECG. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal.*
- Physical examination, vital signs
- Clinical laboratory assessments (hematology, serum chemistries)
- HRCT
- Spirometry (FVC)

- 6MWT and Borg Scale
- Review AEs

4.5.14 Samples for Research Biosample Repository

Not applicable as no samples will be stored in the study. All blood samples drawn for safety assessments will be destroyed immediately after analyzing.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 if it is considered to meet patients' interests best and approved by the Sponsor.

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient for other reasons
- Protocol deviation (at Sponsor's discretion) (e.g. refusal to follow study requirements)

Generally poor compliance in the study will not be treated as a sufficient reason for patient's early discontinuation from the study. However, non-compliant patients cannot proceed in the rollover part of the study, where treatment with pirfenidone is continued in a routine clinical setting.

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. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

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

- Pregnancy
- Unacceptable tolerability and personal safety profile (e.g. adverse events listed in Section 5.1.2, or serious adverse events related to study treatment)

- Patient request or withdrawal of consent
- Patient's early discontinuation from the study (see Section 4.6.1)
- Termination of the whole study by the Sponsor
- Lung transplantation

Patients who receive a lung transplant during the study will discontinue study treatment and the study itself.

If study treatment is discontinued, patients will complete a Follow-up Visit 14-28 days after the last dose of the study treatment. If applicable, discontinued patients should complete all scheduled study assessments and procedures through Week 26.

If early discontinuation of study treatment is being considered, it must be immediately reported by telephone to the Sponosr medical monitor or designee.

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

4.6.3 Study and Site Discontinuation

4.6.3.1 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:

- The incidence or severity of adverse events in this or other ongoing studies of pirfenidone indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Administrative and regulatory reasons.

The Sponsor will notify the investigator if a decision to discontinue the study is made.

4.6.3.2 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:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Pirfenidone is currently approved for medical use in many countries of the world (see Section 1.2). The safety plan for patients in this study is based on clinical experience with pifenidone in completed and ongoing clinical studies and in post-marketing use. The anticipated important safety risks for pirfenidone are outlined below. Please refer to the pirfenidone *instruction for medical use of the medicinal product* for a complete summary of safety information.

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

5.1.1 Risks Associated with Pirfenidone

Pirfenidone has a favourable benefit-risk profile with a well-characterized long-term safety and tolerability profile and manageable side-effects. Pirfenidone does not appear to be associated with unexpected serious adverse events, which could be considered to be life-threatening. Guidelines for management of patients who develop the most common adverse events are provided in Table 3 (see Section 5.1.2).

5.1.1.1 Gastrointestinal Adverse Events

Pirfenidone is associated with a dose response effect regarding gastro-intestinal side-effects notably nausea, vomiting, diarrhoea, dyspepsia. There is a correlation between the maximal plasma concentration of pirfenidone and the incidence of GI adverse events, suggesting that food may reduce the incidence of certain adverse events associated with pirfenidone.

Patients with clinically significant GI symptoms or disease will be excluded from this study (see Section 4.1.2).

5.1.1.2 Skin-Related Adverse Events

Common skin-related adverse events associated with pirfenidone are rash and photosensitivity. The seasonal variation in frequency of skin reactions suggests an association with sun exposure. The underlying mechanism of photosensitivity reactions is likely to be phototoxic and related to the drug ability to absorb both ultraviolet B and A. Pre-clinical data supports that pirfenidone-induced skin reactions are proportional to both light and drug exposure.

Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with pirfenidone. Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Severe photosensitivity reactions are uncommon.

5.1.1.3 Effects on Liver Function Tests

Elevations of ALT and AST > 3 × ULN have been reported in patients receiving therapy with pirfenidone. Rarely these have been associated with concomitant elevations in total serum bilirubin. Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with pirfenidone and subsequently as indicated in the schedule of assessments (see Appendix 1). Patients with significant signs of hepatic impairment will be excluded from the study (see Section 4.1.2).

In case of significant elevation of liver aminotransferases the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines provided in Table 3. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, the following dose adjustments may be necessary.

5.1.1.4 Cardiovascular Safety

The incidence of major cardiovascular events were similar between pirfenidone and placebo groups in pooled population of two clinical studies (ASCEND and CAPACITY). There is no evidence of pirfenidone having a significant effect on QT interval, incidence of arrhythmias and ischemia events. However, pirfenidone should be used with caution in patients treated with other moderate inhibitors of CYP1A2, such as amiodarone and propafenone.

Cardiac function should be monitored with ECG prior to the initiation of treatment with pirfenidone and subsequently as indicated in the schedule of assessments (see Appendix 1). Patients with clinically significant symptoms of cardiac disease will be excluded from the study (see Section 4.1.2).

5.1.1.5 Other Adverse Events

Dizziness

Dizziness has been reported in patients receiving pirfenidone. Patients should know how they react to the study drug before they engage in activities requiring mental alertness or coordination. In clinical studies, most patients who experienced dizziness had a single event, and most events resolved, with a median duration of 22 days.

Fatigue

Fatigue has been reported in patients receiving pirfenidone. Patients should know how they react to the study drug before they engage in activities requiring mental alertness or coordination.

Weight loss

Weight loss has been reported in patients treated with pirfenidone. There was an increase in anorexia and poor appetite but this was not consistently dose related. Investigator should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.

Risks which, were observed in the post-authorization setting:

- Angioedema
- Agranulocytosis

5.1.2 Management of Patients Who Experience Specific Adverse Events

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

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

Event	Action to Be Taken
Gastrointestinal adverse events (nausea, vomiting, diarrhoea, dyspepsia)	Confirm that the study drug is administered with food. If symptoms persist when the drug is taken with food, the dose of pirfenidone should be reduced to 1-2 capsules (267-534 mg) 2-3 times/ day with food. If symptoms resolve, the dose can be re-escalated to the recommended daily dose as tolerated. If symptoms continue, treatment should be interrupted for 1-2 weeks to allow symptoms to resolve. If symptoms continue after temporal interruption, treatment should be permanently discontinued.
Skin-related adverse events (photosensitivity reaction and rash)	Mild to moderate photosensitivity reaction or rash - the dose of pirfenidone should be reduced to 801 mg (3 capsules) per day (267 mg (1 capsule) 3 times a day). Confirm that the patient uses a sunblock daily and avoids sun exposure. If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period. Severe photosensitivity reaction or rash - treatment should be interrupted and medical advice is sought. If the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the investigator.
Elevations of ALT and AST	ALT/ AST elevation > 3 to ≤ 5 × ULN - confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted. Once liver function tests are within normal limits the dose may be re-escalated to the recommended daily dose if tolerated. ALT/ AST elevation to ≤ 5 × ULN accompanied by symptoms or hyperbilirubinaemia (> 2 × ULN) - treatment should be permanently discontinued. ALT/ AST elevation to > 5 × ULN - treatment should be permanently discontinued.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Increased QT Interval	QTcF interval is > 500 ms and/ or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes or in the utmost 24 hours, verified by a study site or local cardiologist. If increase of QT Interval is confirmed, ECG monitoring should continue until QTcF has stabilized on two successive ECGs within 24 h, verified by a study site or local cardiologist. In this case study drug should be interrupted and the patient should be discontinued from study treatment. If QTcF interval is between 500 and 550 msec, confirmed by a repeat ECG within 24 hours, and verified by a study site or local cardiologist, study treatment should be interrupted. If an alternative explanation is identified (e.g., electrolyte abnormality or concomitant medication), re-initiation of study treatment may be considered by the investigator in consultation with the study medical monitor.
Dizziness	If dizziness does not improve within 3-4 weeks or worsens in severity, dose adjustment or even discontinuation of treatment may be warranted.
Fatigue	No action required.
Weight loss	If considered to be of clinical significance, increased caloric intake should be recommended to the patient.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except *exacerbation or worsening of IPF. Worsening of IPF (i.e. IPF progression) is considered as an AE only in case of fatal outcome attributed to this progression (as described in Section 5.3.5.7).*
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)
- Lack of efficacy is not considered as AE

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see *Section 5.3.5.9*)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug or the female partner of a male patient exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/ surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

5.2.3.1 Adverse Events of Special Interest

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

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

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

5.2.3.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be implemented in the study. All adverse events immediately reported to the Sponsor will be reviewed by the IDMC. The IDMC will also review every death case from the point of relationship to the study drug.

The IDMC will conduct regular review of the trial safety data, with the focus on the following safety information:

- Death cases
- Serious adverse events
- Adverse events leading to treatment or study discontinuation
- Unexpected adverse events
- Liver enzyme increases, reported as adverse events

On the basis of the safety data aggregated from different study sites and investigators, the IDMC can recommend discontinuation of the study due to safety concerns.

IDMC members and detailed working regulations are provided in a separate document.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug.

For patients continuing in the rollover part of the study adverse events will be reported until Week 52.

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

5.3.2 Eliciting Adverse Event Information

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

"How have you felt since your last clinic visit/ telephone call?"

"Have you had any new or changed health problems since you were last here/ we talked by the phone?"

5.3.3 Assessment of Severity of Adverse Events

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

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

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

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of IPF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without

preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of IPF, "IPF progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.9 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., to perform protocol required procedures)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Cases when medical aid was provided to the patient in the hospital reception ward

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

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

There is limited clinical experience with pirfenidone overdose. Multiple doses of pirfenidone up to a dose of 4806 mg/day were administered as six 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation period. Adverse reactions were mild, transient, and consistent with the most frequently reported adverse reactions for pirfenidone (Esbriet EMA 2010).

5.3.5.11 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for all sites

Medical Monitor:	[redacted], MD, PhD
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Roche Medical Responsible:	[redacted]
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and

reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and

emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Pirfenidone *Local Instruction for Use*
- Pirfenidone Core Data Sheet

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

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

Additionally, the IDMC will conduct regular review of the trial safety data, as described in Section 5.2.3.2.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Data handling will be the responsibility of Data Matrix. The data will be inspected for inconsistencies by performing validation checks. Any inconsistencies found will be resolved by the monitor after contacting the Investigator. When the data in the database are considered clean and the subjects allocated to subject samples in a data review, the database will be locked to prevent unauthorized access. Next, the database will be made available as SAS® files for statistical analysis.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by Data Matrix and approved by F. Hoffmann-La Roche Ltd. before database lock.

The statistical analysis will be performed by Data Matrix.

The main subject samples of interest are defined as follows.

The 'Allocated to treatment' set will consist of all subjects who:

- Gave their Informed Consent and
- Has successfully completed Screening procedures.

The 'Treated set' (TS) will consist of all subjects who:

- Were in the 'Allocated to treatment' set and
- Received any dose of the study treatment.

The 'Full analysis' set (FAS) will consist of all subjects who:

- *Were included in the 'Treated' set and*
- *Had data for at least one post-baseline assessment of any efficacy measurement.*

6.1 DETERMINATION OF SAMPLE SIZE

Taking into account study design (single group prospective study), sample size was estimated based on feasibility of subject enrollment with precision-based approach. In the ASCEND study primary efficacy endpoint (Percent Predicted FVC) in pirfenidone group changed from 67.8 (11.24) (denoted as mean (SD)) at baseline to 65.3 (14.52) at week 26, with stable disease (decline in FVC < 10 % to 0 %) in 60.1 % of study subjects.

The required sample size *for two-sided 95% confidence level* can be calculated using the following formula:

$$n = \hat{p}\hat{q}\left(\frac{Z_{\alpha/2}}{E}\right)^2;$$

$$n = 0.601 \times 0.399\left(\frac{1.96}{0.125}\right)^2 \approx 58.96.$$

Assuming previous calculations, 60 subjects included in the study will be sufficient for study parameters estimation. Taking into account study goals and the notion that the study drug is a product for the treatment of an orphan drug, margin of error of 0.125 is considered sufficient for parameter estimation. *For precision-based sample size justification, with a sample size of 60 patients, an expected mean value of 2.5% and standard deviation of 20, distance from the mean to limit of the two-sided 95% confidence interval for the mean Change from Baseline to Week 26 (Percent Predicted FVC) will extend about 5 (margin of error). The SD for change from baseline at week 26 is conservatively estimated based on the results of the ASCEND study as standard deviation for Percent Predicted FVC in pirfenidone group at week*

26 (14.52) multiplied by √2 (Machin et al., 1997). This is also in line with the results of CAPACITY programme (Noble et al. 2011) in which the SD of changes from baseline was 17 - 20 at week 72.
Taking into account an expected rate of screening failures about 45%, up to 109 patients will be screened for eligibility.

6.2 SUMMARIES OF CONDUCT OF STUDY

Time-Related Definitions

The baseline period will be defined as the period from Informed Consent to the first study drug administration. The baseline value for a variable in common cases (except efficacy analysis) is defined as the last non-missing value collected before the first study drug administration.

All variables planned to be measured at one or more time points, and supposed to be time-related will be windowed.

Coding Systems

AEs and medical history Investigator terms will be assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT) and primary system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

Prior and concomitant medications will be classified according to active drug substance using the WHO drug dictionary. The generic name, the preferred name and the WHO name will be assigned.

In addition, the Anatomical Therapeutic Chemical (ATC) classes will be assigned to the drug ID. ATC codes are defined to the 4th level. For each medication, the primary ATC class will be assigned manually based on the generic name and the reason for use.

Default Summary Statistics

The default summary statistics for quantitative and ordinal variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. For efficacy data 95% CI will be provided additionally.

Default Frequency Tabulations

For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) will be the default summary presentation.

For AEs and medical history, however, the denominator for the percentage calculation will be the number of subjects at risk. A subject will be considered at risk if the subject is in the *Treated set*.

Subject Listings

Individual subject listings will be produced for all raw data.

Handling missing values

For missing FVC data imputation, patients will be classified into different patterns depending on the availability of data:

Patients with a 26 week FVC value:

1. those who received *study* drug until 26 weeks;
2. those, who prematurely discontinued *study* drug, but who were followed up until Week 26.

Patients without a 26 Week FVC value:

1. those who were alive at 26 weeks;
2. those, who died before 26 weeks.

Missing data at other visits before Week 26 (primary outcome variable) will not be imputed.

The following imputation methods including sensitivity analyses will be applied for patients with pattern 3 - 4:

Assuming that deaths of the patients (pattern 4) is likely to be related to worsening of IPF, these unobserved FVC values should be lower than those in patients who did not die prior to Week 26. Methods for handling missing data due to death will include the following:

- Replacement with the worst possible value (FVC= 0 mL or 0%) (Primary analysis).
- Replacement with worst observed FVC value at week 26 (Sensitivity analysis).

- Replacement with an intermediate value (FVC =1500 mL or 50%) (Sensitivity analysis).

Missing data due to reasons other than death (pattern 3) will be replaced with imputed values based on the average measurements for “similar” patients at that time point (Primary analysis). Similar patients are those without missing data before that time point and whose data have the smallest sum of squared deviations (SSD) from that patient for all visits prior to the one with the missing data. Missing data due to lung transplant will be imputed using the SSD method even if the patient dies after lung transplant. A sensitivity analysis will use the data imputed with last observation carried forward method (LOCF).

Complete case analysis will also be performed as a sensitivity analysis.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race and ethnicity, height, weight, medical history, concomitant medication, serology etc) will be summarized using means, *SD*, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

The assignment of subjects to subject samples, the disposition of subjects with respect to premature termination, reason for premature termination, drug exposure will be summarized.

Medical history, including coding data will be summarized per primary SOC by PT. Additionally medical history will be listed. Protocol deviations will be listed. Prior/concomitant medications will be summarized per Therapeutic or chemical group and preferred WHO name. Additionally prior/concomitant medications will be listed.

6.4 EFFICACY ANALYSES

The *FAS* set will be used for the efficacy analysis. All efficacy parameters *will be* summarized with descriptive statistics (mean, *SD*, median, minimum maximum, 95% CI) for each measurement time point.

6.4.1 Primary Efficacy Endpoint

The primary outcome variable is the absolute change in FVC from Baseline to Week 26 (both in mL and % predicted). Baseline FVC will be the average of the highest FVC measurement recorded at the Screening and Day 1 visits. The FVC at Week 26 will be the average of the highest FVC measurement recorded on two separate days at Week

26. Data will be analyzed using a standard descriptive statistics for continuous variables and 95% CI for the mean.

The data imputation methods for primary endpoint are described in Section 6.2.

The distribution (number and percentage) of primary outcome variable by patients across *three* categories of change from Baseline (Decline of ≥10% or death before Week 26; *Decline of < 10% to 0%;* Improvement of ≥ 0%) will be provided in frequency table.

Additionally, the absolute change in FVC from Baseline at Week 12, 39 (optional) and 52 (optional) and mean FVC change through all time endpoints (both in mL and % predicted) will be summarized in tables with standard descriptive statistics for continuous variables and 95% CI for mean.

6.4.2 Secondary Efficacy Endpoints

Change in 6MWT distance from Baseline to Week 26

Baseline 6MWT distance will be the average of the measurements recorded at the Screening and Day 1 visits. The 6MWT distance at Week 26 will be defined as the average of the 6MWT distance recorded on two separate days at Week 26. Data will be analyzed using a standard descriptive statistics for continuous variables and 95% CI for mean.

The distribution (number and percentage) of 6MWT distance by patients across two categories of change from Baseline (Decline of ≥ 50 m or death before Week 26; Improvement of ≥ 0 m) will be provided in frequency table.

Additionally, the absolute change in 6MWT from Baseline at Week 39 (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for mean.

Change from Baseline to Week 26 in patients' quality of life as measured with EQ-5D-*5L*

Results of EQ-5D-*5L* questionnaire will be summarized in two ways:

- Cross tabulation for each of five dimensions (Mobility, Self-Care, Usual Activities, Pain / Discomfort, Anxiety / Depression) by response and study week.
- VAS score, including changes from baseline, will be summarized with descriptive statistics (mean, standard deviation, median, minimum and maximum) for study week.

Additionally, a single *Index* score will be provided, if necessary.

6.4.3 Exploratory Efficacy Endpoints

HRCT fibrosis score

The HRCT findings will be evaluated using HRCT scoring system. One ILD radiologist will make assessments of 4 main findings in three zones of each lung. The six zone scores will be averaged to determine the total score for each patient. Score will be recorded at the initial diagnosis and after six and 12 months in a similar manner for further comparison. The mean ± SD of HRCT fibrosis score like continuous variable will be determined obligatory at baseline, 6 *months* and optional at 12 months.

The values of HRCT fibrosis score at baseline, at Week *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for the mean.

Additionally, the absolute change of HRCT fibrosis score from baseline at Week *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for the mean.

The paired t-test will be performed to evaluate the changes in the variable from the baseline to Week *26* (optional) and Week 52 (optional), respectively. The type I error rate will be set to 5%.

Lung opacity (ground-glass attenuation)

The sign 'lung opacity' will be qualified separately using methodology described above for other signs, and its change over time will be assessed outside the framework of a total summed index of fibrosis (HRCT fibrosis score). Lung opacity should be graded as reticular abnormality to calculate the score for each zone, i.e. the percentage (%) area of opacity in a zone should be multiplied by the score of 2.

The percentage area of opacity at Baseline, at Week *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

Additionally, the absolute change of percentage area of opacity from Baseline at Week *26* (optional) and Week 52 (optional) will be summarized in table with standard descriptive statistics for continuous variables and 95% CI for *the* mean.

Exacerbations

An exacerbation will be defined as an AE with special criteria*, i.e. only in case the exacerbation has led to death of a patient (see Section 5.2.1)*. Rate of exacerbation will be reported in three following tables:

- Exacerbation cases during treatment period (until Week 26).
- Exacerbation cases during long-term follow-up period (from Week 26 to Week 52).
- Exacerbation cases during whole study period (from Day 1 to Week 52, applicable only for subjects continuing in the rollover study).

Exacerbation cases will be listed.

6.5 SAFETY ANALYSES

The *Treated set* will be used for the analysis of the safety and tolerability data.

Study treatment is defined as pirfenidone 2403 mg/d administered in divided doses TID with food. Study treatment will be titrated over 14 days to the full dose of 9 capsules per day (three 267-mg capsules taken orally TID with food). Patients will remain on a stable maintenance dose for the duration of the treatment period unless the dose is reduced to manage an AE or titrated again when restarting study treatment after a 28-day or greater interruption in treatment.

AEs will be reported on a per-subject basis, i.e. counting subjects rather than events. Only treatment emergent AEs will be reported. In the listings, however, all occurrences of the AEs will be presented.

Treatment emergent AEs will be summarized per primary *SOC* and *PT*. Severity and drug-event relationship of treatment emergent AEs will be summarized separately.

Vital signs, including changes from baseline will be listed *and* summarized with descriptive statistics (mean, *SD*, median, minimum and maximum) for each measurement time point. Out-of-range values with assessment of clinical significance will be provided in frequency tables.

Results of ECG, including changes from baseline will be listed *and* summarized with descriptive statistics (mean, *SD*, median, minimum and maximum) for each measurement time point. Out-of-range values with assessment of clinical significance will be provided in frequency tables.

Laboratory variables, including changes from baseline will be listed and summarized with descriptive statistics (mean, SD, median, minimum and maximum) for each measurement time point. Additionally, shift tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point will be provided.

Results of physical examinations will be summarized in corresponding frequency table and listing.

6.6 INTERIM ANALYSIS

No interim analysis is planned in the study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Data Matrix will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the data manager 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. Central laboratory data and HRCT data will be sent directly to the Sponsor, using the Sponsor's or vendor's standard procedures to handle and process the electronic transfer of these data as appropriate.

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 ELECTRONIC PATIENT- AND OBSERVER-REPORTED OUTCOME DATA

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

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before 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, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The 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 and the distribution of IMP, including eCRFs, electronic PRO and ObsRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the 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, and the laws and regulations of the country in which the research is conducted. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

The study will be conducted in accordance to the following local regulations of the Russian Federation as ammended: FL #323-FZ “On fundamental principles of healthcare in the Russian Federation” dated 21-Nov-2011; FL #61-FZ “On drug circulation” dated 12-Apr-2014; Government resolution of the Rusian Federation #714 “On the approval of model rules of mandatory health and safety insurance for patients participating in clinical studies” dated 13-Sep-2010; Decree of the Ministry of Healthcare #774n “On Ethics Committee” dated 31-Aug-2010; Decree of the Ministry of Healthcare #200n “On the approval of the rules of Good Clinical Practice” dated 01-Apr-2016; National Standard “Good Clinical Practice”. GOST P 52379-2005 dated 27-Sep-2005.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. It will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final 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 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).

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

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. Patients' confidentiality will be observed in accordance with the relevant Russian regulations.

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 the analyses, data derived from exploratory biomarker specimens 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.

8.5 INSURANCE

Patient insurance in the study will be performed in accordance with the Russian regulatory requirements. All patients will be provided with personal insurance policies as participants of the clinical study. All patients will be informed about health insurance at the signing the Informed Consent procedure and will be issued with the personal policy as soon as the identification number is attributed to an individual patient. Details on patient insurance will be provided in the Informed Consent Form.

8.6 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

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.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' 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

Administrative structure of the study is presented below.

Sponsor:	F. Hoffmann-La Roche Ltd., Switzerland, *Representative Office of F.Hoffmann-La Roche Ltd.* Phone/ Fax: *Tel:* [redacted] */ Fax:* [redacted] Address: *Trubnaya sq., 2 "Neglinnaya Plaza" Business Center, 107031, Moscow, Russia*
Sponsor's Medical Monitor:	[redacted], MD, PhD IPHARMA LLC 5, Nobel str., Skolkovo, *143026,* Moscow, Russia Tel.:+ 7 (495) 276-11-43 / Fax: + 7 (495) 276-11-47 [redacted]
Investigational Sites:	See *site* list
Coordinating Investigator:	[redacted], Doctor of Medical Sciences, Professor [redacted] *Russia* Tel.: [redacted] / Fax: [redacted]
Contract Research Organization:	Quintiles GesmbH, Representative Office in Russia, 37A-14 Leningradsky prospect, *125167,* Moscow, Russia
Data Management:	Data Matrix Ltd *14 Nekrasova Street, Let. A, 191014,* Saint Petersburg, Russia Tel.: +7 (812) 449-86-33 / Fax +7 (812) 449-86-35 info@dm-matrix.com
Central CT scan reviewers:	[redacted], **MD, Professor.** [redacted] Moscow [redacted], **MD, Professor.** [redacted]

Central biopsy reviewers: [redacted] Moscow
[redacted] **MD, Professor.** [redacted]
[redacted], Moscow
[redacted], **Ph.D.** [redacted]
[redacted] Moscow.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

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

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

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

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

Study period	**IC visit**	**Screening (Washout, if applicable)**	**Treatment period**										**Follow-Up**	**Long-Term Follow-Up[16]**	
Week/ Day (Window)	-	–4 to –1 W	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 2 d)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Informed consent[1]	x														
Phone Call Assessment[2]				x											
Demographic data		x													
Medical history, concomitant medication[3]	X[3]	x[3]	x		x	x	x	x	x	x		x	x		
Vital signs, physical exam[4]		x	x		x	x	x	x	x	x	x	x	x	x	x
Height, weight[5]		x	x		x	x	x	x	*x*	*x*		x	x		
ECG[6]		x	x			x	x					x			x
Eliciting AEs		x	x	x	x	x	x	x	x	x		x	x	x	x
Disease Assessment and PFT															
Review SLB[7] (if applicable)	x														
Review transbronchial lung biopsy/BAL[8]		x													
Review HRCT[7]	x														
HRCT		x[9]										x			x
Spirometry (FVC)[10]		x	x					x			x	x		x	x
DLco		x													
6MWT		x	x					x			x	x		x	x
Laboratory Tests															
Hematology, blood chemistry[11]		x	x		x	x	x	x	x	x		x	x	x	x
Serologic tests[11]		x													

Study period	IC Visit	Screening (Washout, if applicable)		Treatment period										Follow-Up	Long-Term Follow-Up[16]
Week (Window)		–4 to –1	Day 1	W1 (± 1 d)	W2 (± 2 d)	W4 (± 2 d)	W8 (± 2 d)	W12 (± 1 w)	W16 (± 1 w)	W20 (± 1 w)	W26 (± 1 w)		14–28 days after last dose	W39 (± 2 w)	W52 (± 2 w)
Pregnancy test		x	X[12]			x	x	x		x		x			
PROs and ClinROs															
GAP assessment		x													
Borg scale[13]		x	x					x			x	x		x	x
EQ-5D questionnarie[13]		x	x					x				x			x
Patient diary (review, dispense)[14]		*x*	x	x	X	x	x	x	x	x		x			
Telephone calls (IPF Care program)[15]															

[1] Written informed consent must be obtained prior to any study-associated procedure, including discontinuing any prohibited medications.

[2] Safety-related information (AEs) and adherence to treatment is collected.

[3] Complete medical history is collected at *an IC visit*, washout and screening only. Thereafter, directed history (including review of AEs/SAEs, concomitant medications, oxygen use, hospitalizations, dosing, and diary) is only collected.

[4] Complete physical examination is performed at the Screening only (head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems). At subsequent visits (or as clinically indicated), only limited, symptom-directed physical examinations should be performed.

[5] Height is assessed at the Screening only.

[6] ECG should be performed after patient's resting in a supine position for at least 10 min, prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws), bronchodilator administration and within 3 hours after any meal)

[7] To confirm IPF will be applicable to use previously performed HRCT, if it is performed not earlier than 24 months before the Screening. Review of the SLB samples obtained within 4 years before the Screening should be performed centrally for elig bility confirmation. Histopathological evaluation, if not available, is not repeated at the Screening.

[8] Transbroncheal biopsy or BAL are not mandatory and will only be reviewed at the Screening, if available, to exclude other causes of PF.

[9] HRCT should be performed at the Screening only for patients having no validated procedure within 2 months prior initiation of treatment.

[10] At screening, spirometry measurements of FVC should be performed before and after administration of albuterol (or sa butamol) from a metered dose inhaler (4 separate doses of 100 mg). Tests should be repeated after a 15-min delay. During further visits, bronchodilator test is not necessary to perform. Collection and recording of the retrospective FVC values obtained in clinical practice over the last year will be performed only *at the* screening visit.

[11] Blood samples must be drawn in fasted state. *Serologic tests: rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibody titer.*

[12] Pregnancy test must be performed before first dosing on Day 1 and must be negative. If the urine test is positive, serum pregnancy test must be performed.

[13] Questionnaires should be self-administered before the patient or clinician receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, with the exception for Borg scale administered in conjunction with the 6MWT.

[14] Patient diary should be filled out on daily basis by the patient and reviewed by the investigator at in-clinic visits. Patient diary captures information on compliance and AEs occurance and is dispensed as needed.

Appendix 1
Schedule of Activities (cont.)

[15] Schedule of calls in IPF Care Program you can see in Appendix 7
[16] Only in patients continuing treatment with pirfenidone in real clinical practice.

Appendix 2
HRCT Protocol

For IPF assessment in the current clinical trial a spiral CT scanning (continuous, or volumetric scanning) should be utilized. HRCT acquisition should only be performed with multidetector CT scanners with at least 16 slices per gantry rotation capacity.

HRCT scans are usually obtained with the patient in supine position, with hands on the nape, in a single unforced breath hold. Scanning is normally directed upward (from feet to the head) in order to attenuate breathing artefacts in the basal parts of lungs. The key technical requirements are acquisition collimation < 1 mm (opposite regular 0.65-0.8 mm), reconstruction parameters: 1 mm-slices, reconstruction interval 1 mm, high resolution imaging, lung window, imaging field is adjusted to the chest volume. Dose detection software should be utilized to decrease radiation exposure of the patients. Key technical requirements for spiral HRCT are summarized in the Table 1-1.

Expiratory CT scanning

Expiratory CT scanning aims to refine the differential diagnosis of IPF with hypersensitivity pneumonitis and obstructive lung diseases. Expiratory CT scanning is performed after forced expiration and breath hold. Other scanning parameters remain unchanged. Expiratory CT scanning is utilized to disclose coexisting air trapping resulting from impaired expiration air flow in small bronchi. Expiratory CT scanning is performed only after inspiratory CT acquisition when existing obstructive changes are similar to restrictive respiratory signs. Expiratory CT scanning is performed with the same technical parameters.

Prone CT scanning

Prone CT scanning is utilized to repair functional hypoventilation of the lower lung lobes at inspiration. It causes development of the ground-glass opacities along the dorsal surface of the chest. This manoeuvre is of high importance in patients with suspected IPF, as absent or insignificant ground-glass opacities distinguish IPF from other UIPs. Prone CT acquisition must be performed only after basic HRCT and at presence of the ground-glass opacities along the dorsal surface of the lung as revealed with the supine scan.

Appendix 2

HRCT Protocol (cont.)

HRCT for response assessment and follow-up

Besides diagnosic purposes, HRCT is utilized in the study for response assessment and follow-up. HRCT is perfomed at initiation of the participation in the study and at the end of treatment. Adherence to the same technical parameters of acquisition, including posture, inspiration volume, imaginfg field, tube current and collimation, reconstruction interval, is the main requirement for repeated scanning in the course of the study. HRCT readings must not be assessed against X-ray scans. If the patient does not have X-ray scan at disease onset or at certain relevant timepoints the subsequent assessments should be performed with HRCT. HRCT frequency in the study is not strictly regulated.

Appendix 2

HRCT Protocol (cont.)

Table 1-1. Spiral scanning.

Parameter	< 16 slices per gantry rotation	≥ 16 slices per gantry rotation	< 16 slices per gantry rotation	≥ 16 slices per gantry rotation
Collimation (slice thickness)	1.25 mm	0.6-0.8 mm	1-1.5 mm	0.6-0.8 mm
Slice interval	1 mm	0.6-0.8 mm	10 mm	0.6-0.8 mm
Reconstruction algorithm	High resolution (bony)		High resolution, high spatial resolution algorithm, bony algorithm	
Spot reconstruction (field of vision, FOV)	Total lung volume		Total lung volume	
Level of inspiration	Unforced breath hold		End inspiration	
Physical parameters	120 kV/ automatical exposure		120 kVp / care dose	
Scanning time	As low as practicable for the scan (< 0.75 sec)		< 0.75 sec	
Window (level/ width)	-500…-700/1500 HU (Hounsfield unit) lung window		Pleural (lung) window	
Possible windows (level/ width)	-850/900 HU emphysema and cystic airspaces assessment +35…+45/400 HU mediastinal window		Lung window Soft window	
Recording/ archiving	CD/ DVD record in DICOM formate and imagery viewer software Link to the cloud archive storage			

High-Resolution Computed Tomography Criteria for UIP Pattern

Morphologically IPF is based on the lung abnormalities typical for UIP. X-ray/ CT scans of patients with IPF are characterized by morphological abnormalities in lungs, i.e. UIP. The picture is characterized by various signs, typical or not typical for UIP (see Table 1-

Appendix 2

HRCT Protocol (cont.)

2). These signs may a) be of different severity (varying from apparent to unlikely, marginally detectable) and b) be present in a variety of combinations. The main diagnostic role is hardly played by separate signs but by their clinically significant combinations. Radiological conclusion is always based on probability: typical, possible or inconsistent UIP picture.

Table 1-2. HRCT Criteria for UIP Pattern

Typical (apparent) UIP pattern (all 5 features)	• Possible UIP Pattern (All 3 Features)	• Inconsistent with UIP Pattern (Any of the 7 Features)
• Cortical, basal predominance • Diffuse reticular abnormality • Honeycombing • Traction bronchiectasis • Absence of any features contradictory to this pathology •	• Cortical, basal predominance • Diffuse reticular abnormality • Absence of any features contradictory to this pathology •	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground-glass abnormality (extent greater than reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, away from areas of honeycombing) • Consolidation in bronchopulmonary segment(s)/lobe(s)

Typical (definite) UIP pattern implies combination of the following HRCT signs:

- cortical and basal predominance of abnormalities in the lungs;
- diffuse bilateral reticular abnormalities with
    - small subpleural air cysts (honeycombing);
    - traction bronchiectasis;
- absence of untypical HRCT features of the pathology.

Appendix 2

HRCT Protocol (cont.)

Revealing all four sings listed above with great probability supports the presence of UIP. In case the key signs – honeycombing and traction bronchiectasis - are absent HRCT pattern of UIP is only possible (probable) and further management of the patient, primarily indication for lung biopsy and initiation of treatment, should be discussed by the MDT members.

Typical UIP patern on HRCT is not specific for IPF only. It can be observed in patients with other diseases, particularly of known etiology, when lung abnormalities form UIP pattern. Examples are systemic connective tissue diseases, various environmental exposures and domestic factors (e.g. chronic hypersensitive pneumonitis), drug toxicity. It is impossible to ascertain these diseases on the basis of X-ray or HRCT examination only. Therefore, it is not recommended to use the term “idiopathic” in the description of the investigation procedure and conclusion. The main responsibility of the radiologist is to reveal or rule out typical UIP pattern, which should be stated in the conclusion.

Disposition of abnormalities in the lungs

Cortical predominance of lung abnormalities with amplificatiom from upper lungs to diaphragm is typical for IPF. The most prominent changes localize subcortically along the costal and diaphragmal pleura. Basal predominance forms the so called anteroposterior gradient when lung changes amplify from the front to the back of the chest. Abnormal parts of the lungs are independent from lobar or segmental margins. As a result, typical disposition of abnormalities in IPF is cortical and basal which can be distinctly observed on the series of axial tomograms and multiplanar reformation. Approximately 10 to 15% of patients with IPF have abnormalities in the upper lungs which makes the pattern not typical and complicate diagnostics.

Honeycombing

Honeycombing is a group of subpleural air cysts, usually similar in diameter of about 2-3 to 10 mm, sometimes more than 2.5 cm. These cysts are round-shaped, with closed cavity and distinct demarcation, which differs them from bronchiectasis. Cyst diameter and wall thickness may vary significantly; however, the cavities look typical. Honeycombing symptom is the main, one of the most significant, CT signs of the lung fibrosis of any etiology. But predominance of the cysts along the visceral pleura,

Appendix 2

HRCT Protocol (cont.)

especially their multilayer location, diaphragm-oriented increment of abnormality are typical specifically for UIP.

Traction bronchiectases

Traction bronchiectases are uneven dilation of the bronchi and bronchioles as a result of the fibrotic shrinkage of the lung. Dilated bronchi may look like air strips with thin uneven (wavy) walls. Transversal dimension may show bronchi as cysts and bronchiole as microcysts in the peripheral parts of the lung. Location of the multiple air cysts around dilated bronchi may confound differentiation with the honeycombing symptom. Multidimensional reformations should be used for proper understanding of the morphological substrate.

Reticular abnormality

Reticular abnormality is a net of relatively thin lines, round- or polygon-shaped, on unchanged lung tissue or moderate lung opacity. Anatomically these lines represent abnormal interstitial lung elements resulting from intralobular interstitial tissue (less than 2 cm in size) thickening in UIP. These structures are usually presented with the fragments of acini septa. Septal lines (acini septa of a larger size), 1-2 cm in diameter, can also be involved in reticular abnormalities; however, they are usually less affected than smaller reticular elements.

Lung opacity (or ground-glass attenuation)

Lung opacity (or ground-glass attenuation) is a HRCT scialogical phenomenon characterized with mid-enhanced density of lung tissue, with lumina and walls of the bronchi, lung vessels, as well as foci and reticular abnormalities, if present. Morphological substrate of the lung opacity symptom is formed by the changes in the lung tissue with unaffected airness which are not captured by the CT acquisition. These changes may include thickening of the alveolar septa of any etiology, partial alveolar filling with different contents, alveolar shrinkage due to hypoventilation, enhanced lung perfusion and lung congestion. When honeycombing and traction bronchiectasis are not revealed, lung opacity may be one of the signs of active inflammation. When honeycombing and traction bronchiectasis are present, lung opacity is usually a sign of interstitial lung fibrosis.

Appendix 2

HRCT Protocol (cont.)

IPF exacerbations and complications

IPF exacerbation is characterized with appearance of new sites of lung opacity-like density and/ or sites of consolidation, or abrupt and fast exaggeration of the present alike abnormalities. Infiltration overlaps cortically on reticular abnormalities and honeycombing. In some cases honeycombing reduces partially or completely due to effusion in the cysts.

Assessment of UIP signs

Assessment of UIP signs on HRCT will be performed using a semiquantitative method (see Table 1-3). Each lung will be divided vertically into three zones: upper zone, middle zone and lower zone. Margins between the zones on axial section are level of tracheal bifurcation and level of the right lower pulmonary vein. The upper lung zone is defined as the area of the lung above the level of the tracheal bifurcation, the lower lung zone is defined as the area of the lung below the level of the lower pulmonary vein and the middle lung zone is defined as the area of the lung between the upper and lower zones.

The HRCT findings will be graded on a scale of 1-4 based on the classification system: 1) normal attenuation; 2) reticular abnormality; 3) traction bronchiectasis; and 4) honeycombing. The presence of each of the above four HRCT findings should be assessed independently in three (upper, middle and lower) zones of each lung. The extent of each HRCT finding will be determined by visual estimation of the percentage (%) (to the nearest 5%) of parenchymal involvement in each zone, from 0 to 100. A total sum of all abnormalities in one zone of a lung cannot exceed 400%.

The score for each zone will be calculated by multiplying the percentage of the area by the mentioned above grading scale score (1-4). The zone scores for six zones of two lungs will be averaged to determine the total score for each patient. The overall HRCT score should be obtained by adding the averages for each index. The highest possible score is 400 points and the lowest score is 100 points using this calculation method.

The total score will be named as the “HRCT fibrosis score”. Semiquantitative assessment with HRCT fibrosis score calculation will be performed at initiation of treatment and 6 months later. For patients continuing therapy in real clinical practice after study completion additional assessment will be performed in a year of therapy.

Appendix 2

HRCT Protocol (cont.)

Table 1-3. Assessment of HRCT UIP signs in lungs.

Sign	Reticular abnormality	Honeycombing	Traction bronchiectases	Normal attenuation	Lung opacity
Upper zone RL[1]					
Middle zone RL					
Lower zone RL					
Upper zone LL[2]					
Middle zone LL					
Lower zone LL					

[1] RL – right lung.

[2] LL – left lung.

The sign 'lung opacity' will be qualified separately using methodology described above for other signs, and its change over time will be assessed outside the framework of a total summed index of fibrosis (HRCT fibrosis score). Lung opacity should be graded as reticular abnormality to calculate the score for each zone, i.e. the percentage (%) area of opacity in a zone should be multiplied by the score of 2.

References

Ichikado K, Suga M, Müller NL et al. *Acute interstitial pneumonia: c*omparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002, 165:1551–6.

Oda K, Ishimoto H, Yatera K et al. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. Respir Res 2014,15:10.

Appendix 3
Histopathologic Criteria for UIP Pattern

UIP Pattern (All 4 Criteria)	Probable UIP Pattern	Possible UIP Pattern (All 3 Criteria)	Not UIP Pattern (Any of the 6 Criteria
• Evidence of • marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis/ architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) **or** • Honeycomb changes only[c]	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (see UIP Pattern column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Hyaline membranesa • Organizing pneumonia[a,b] • Granulomas[b] • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

[a] Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.

[b] An isolated or occasional granuloma and/ or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

[c] This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

Appendix 5

EuroQol-5D Questionnarie (cont.)

Reference

American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/ Latin American Thoracic Association. 2011. An official ATS/ERS/ JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183:1–38 [In press].

Appendix 4
Borg Scale

This instrument is to be self-administered by the patient as part of the 6MWT procedure. The patient will be given a paper copy of this instrument with the following instructions given in writing at the time the instrument is administered:

“Please rate the current severity of your breathlessness by circling the most appropriate number on the following scale.”

0 Nothing at all

0.5 Very, very slight (just noticeable)

1 Very slight

2 Slight (light)

3 Moderate

4 Somewhat severe

5 Severe (heavy)

6

7 Very severe

8

9

10 Very, very severe (almost max)

Reference

Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982, 14,5:377–81.

Appendix 5
EuroQol-5D-$5L$ Questionnarie

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 ❑

Appendix 5

EuroQol-5D Questionnarie (cont.)

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 ❑

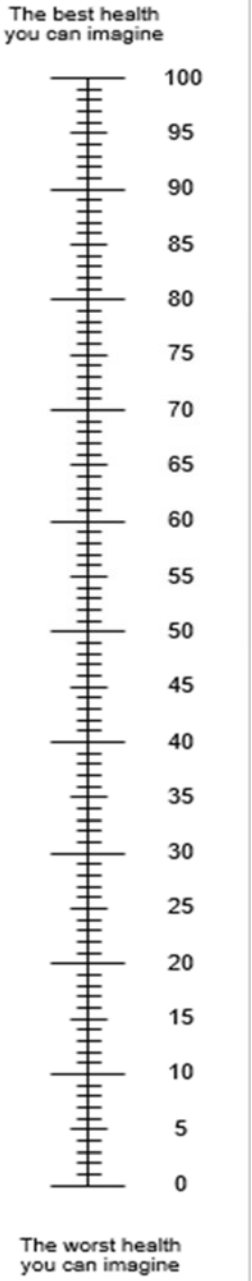
I am extremely anxious or depressed ❑

Appendix 5

EuroQol-5D Questionnarie (cont.)

- 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 = ☐



Appendix 5
EuroQol-5D Questionnarie (cont.)

References

EuroQol Group. Web-source [Available at:https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-on-paper/]

Appendix 6
GAP Risk Assessment

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, % *predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, % *predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

Figure Legend

The GAP index and staging system.

Points are assigned for each variable of the scoring system to obtain a total point score (range, 0–8). Patients should be scored in the "Cannot perform" category for DLco if their symptoms or lung function prohibited performance of the DLco maneuver. If Dlco is unavailable because it was not ordered or not completed because of nonrespiratory limitations, then the model cannot be applied. The total point score is used to classify patients as stage I (0–3 points), stage II (4–5 points), or stage III (6–8 points). Model-

Appendix 6
GAP Risk Assessment (cont.)

predicted 1-, 2-, and 3-y mortality is shown by stage. GAP = gender, age, and 2 lung physiology variables (FVC and DLco).

The formulas for computing predicted DL_{CO} are as follows (Crapo and Morris 1971):

Predicted DL_{CO} for men 0.410 × height (cm) − 0.210 × age (yr) − 26.31

Predicted DL_{CO} for women 0.282 × height (cm) − 0.157 × age (yr) − 10.89

References

Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis 1981,123;2:185-9.

Ley B, Ryerson CJ, Vittinghoff E et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012,156:684-91.

Appendix 7

IPF Care Program

IPF Care Program by F. Hoffmann-La Roche Ltd (Switzerland)

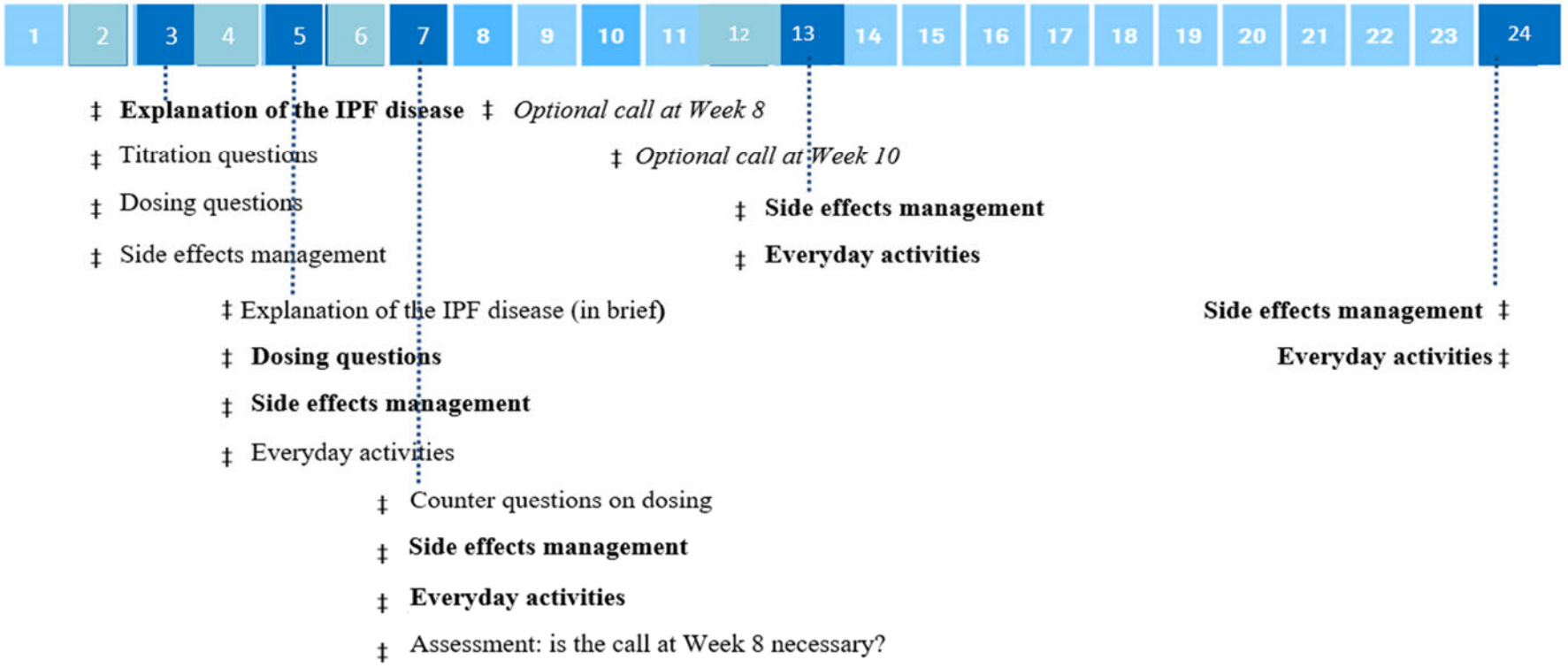
Guidance for telephone calls to the patients participating in the clinical trial of pirfenidone

Telephone calls are scheduled at Weeks 3, 5, 7, 13 and 24. Optional calls can be performed at Weeks 8 and 10, if necessary.

A total number of calls is 5 to 7. Schedule of telephone calls and topics for discussion are detailed in the Figure below.

Appendix 7

IPF Care Program (cont.)



Answers to the questions in accordance with FAQ – IPF Care Program

A full version of the IPF Care Program will be supplied by the Sponsor to the investigators or other designated staff.