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

NCT Number: NCT02951429

Document Date: Protocol Version 2: 01-Dec-17

PROTOCOL

TITLE:	**A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SILDENAFIL ADDED TO PIRFENIDONE IN PATIENTS WITH ADVANCED IDIOPATHIC PULMONARY FIBROSIS AND *RISK* OF GROUP 3 PULMONARY HYPERTENSION**
PROTOCOL NUMBER:	MA29957
VERSION NUMBER:	*2*
EUDRACT NUMBER:	2015-005131-40
IND NUMBER:	67284
TEST PRODUCTS:	Pirfenidone (RO0220912) and sildenafil (RO0280296)
MEDICAL MONITOR:	[redacted] MD
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1 (19-July-2016)
DATE AMENDED:	Version *2*: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	*[This space is reserved for the electronic signature]* Title	Date and Time (UTC)
[redacted]	Company Signatory	01-Dec-2017 13:33:46

PROTOCOL AMENDMENT, VERSION 2.0:
RATIONALE

Protocol MA29957 has been amended to reflect the feedback received after the start of the study from the Steering Committee, sites or ethic committees. The changes to the protocol along with a brief rationale for each change are summarized below:

- Title, Sections 1.2, 1.3, 2, 3.1, 3.3.2, 3.3.5, 4.1, 4.1.1, and 6.4.1, Figure 2, and Figure 3 were updated to clarify the terminology related to characterization of the eligible patient population. The term "intermediate or high probability" of Group 3 pulmonary hypertension reflects the 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guideline and it is related to echocardiography assessments. As in this study, the patients are eligible based on right heart catheterization (RHC) or ECHO data, the terminology "risk of Group 3 pulmonary hypertension" is considered more appropriate. Hence throughout the protocol, when describing the eligible population "intermediate or high probability" of Group 3 pulmonary hypertension was changed to "risk" of Group 3 pulmonary hypertension.

- Section 1.3 was updated to include collection from randomized patients of the most recent high-resolution computed tomography (HRCT) scans performed prior to entering the study. Following availability of data from the RISE-IIP study (Nathan et al 2016, ERS) which showed an increased incidence of death both from the main study and the open-label extension period, the intention is to collect HRCT from randomized patients to support, if considered necessary, an in-depth analysis of any case of death in the current study. Moreover in view of the fact that results from RHC which allows to characterize the severity of pulmonary vascular disease will be available only in small proportion of patients (majority of the patients so far being eligible are based on ECHO data), having the possibility to potentially evaluate baseline HRCT for signs of pulmonary vascular disease might be considered relevant for the study.

- Section 3.1 was updated to include clarification to the text that the washout period can be part of the Run-in period, if the Run-in period is applicable. In the protocol version 1, this text was provided only as a footnote to Figure 1. This has been added now also to the text.

- Section 3.1 was updated to include also region Asia-Pacific, as potentially, additional countries might join the study.

- Sections 3.1, 3.2, and Figure 1 have been clarified in the protocol that the study ends when all patients complete the overall 12 months safety follow-up period, i.e. 4 weeks follow-up after end of treatment at week 52 plus additional 11 months safety follow-up after the Follow up visit at week 56. Thus, depending on the

wording in the protocol, in some instances the follow-up period had to be updated from “12” to “11” months.

- Section 4.1.2 additional exclusion criteria based on Sildenafil Safety Reference Information # 7 (severe hypotension [BP <90/50 mmHg]) was removed based on Sildenafil Safety Reference Information as this is already covered by the main exclusion criteria 4, i.e. “Hypotension (blood pressure [BP] <100 mmHg systolic or <50 mmHg diastolic), autonomic dysfunction, or conditions in which vasodilation may cause an unsafe drop in blood pressure”.

- Section 4.1.2 additional exclusion criteria based on Sildenafil Safety Reference Information #10 (use of an alpha blocker) was removed based on Sildenafil Safety Reference Information. Alpha blockers are not contraindicated as per the sildenafil label. Moreover, benign prostatic hyperplasia is a condition quite common in the study population's age group. Nevertheless, the protocol highlights repeatedly that these patients should be treated with caution. Section 4.3.2.3.2 highlights the fact that patients should be treated with caution if they are receiving alpha-blockers or other antihypertensive medication. Section 5.1.2.7 states that "Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the co-administration may lead to symptomatic hypotension in susceptible individuals. To minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Physicians should advise patients what to do in the event of postural hypotensive symptoms.”

- Sections 4.1.2 and 4.4.2 were updated to reflect the correct terminology related to “Guanylate cyclase stimulators” from “Guanylate cyclase inhibitors”

- Section 4.5.5 has been clarified that in few countries with local requirements (e.g. Egypt, UAE) local laboratory assessments will be performed.

- Section 4.5.16 has been clarified that Sildenafil/placebo could be stopped temporarily or permanently, according to the judgment of the Investigator, in case of patients with systolic blood pressure (SBP) <100 mmHg or diastolic blood pressure (DBP) <50 mmHg

- Section 6 and Section 6.4.1. were updated to clarify the “safety population” definition in line with the independent Data Monitoring Committee (iDMC) charter. The “per protocol” population definition has been deleted as sensitivity analysis of the primary endpoint will be conducted based on the intent-to-treat (ITT) population and will include more parameters, not only the per protocol population. Details will be added in statistical analysis plan.

- Section 10 reference list was updated to reflect the requirement to refer to current version of the IB.

- Appendix 1 (Schedule of Assessment) has been updated to reflect changes in the protocol. In addition, footnotes related to FVC, DLCO and ECHO assessments have been updated based on the feedback received from the countries regarding the difficult aspect of scheduling two appointments very close to each other for the same assessment. The note has been added to reflect that in case ECHO/spirometry at screening collect all information required at Visit 1 and the patient is eligible and randomized in ≤14 days, the screening ECHO/spirometry can be used as baseline assessment.

The above changes have also been made to the Synopsis and study Informed Consent Form, as applicable.

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

PROTOCOL AMENDMENT, VERSION 2.0:
SUMMARY OF CHANGES

PROTOCOL TITLE:

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

PROTOCOL SYNOPSIS

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

SECTION 1.2: BACKGROUND ON TEST PRODUCTS

The test products in this Phase IIb trial will be pirfenidone (Esbriet®) and sildenafil (generic formulation). Patients will have advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH, which is considered to be secondary to IPF, and be on a stable dose of pirfenidone with demonstrated tolerability.

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

In study MA29957, patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH will be included. To address potential concerns regarding the RISE-IIP premature termination, but most importantly to minimize any potential risk in the study patient population in MA29957, a safety plan has been put in place for this study. The safety plan includes: appropriate eligibility criteria, dose modification and/or discontinuation guidelines for each identified and potential risk (see Section 5.1), *collecting from randomized patients the most recent HRCTs performed prior to entering the study,* monitoring of patients at risk as well as the regular monitoring of patient data by an iDMC. Moreover, the long-standing experience available with sildenafil should also be considered.

SECTION 2: OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety and tolerability of sildenafil compared to placebo added to pirfenidone treatment in patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH.

SECTION 3.1: DESCRIPTION OF THE STUDY

This is a Phase IIb, randomized, placebo-controlled, multicenter, international study of the efficacy, safety, and tolerability of combination treatment with sildenafil and pirfenidone in patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH, who have been on pirfenidone in a dose range of 1602 to 2403 mg/day with

demonstrated tolerability. For the purposes of this study patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH have to present with:

- advanced IPF as defined by a measurable DLCO ≤40% of predicted value at Screening;

AND

- ~~intermediate or high probability~~ *risk* of Group 3 PH as defined by
    - mean pulmonary artery pressure (mPAP) ≥20 mmHg together with pulmonary artery wedge pressure (PAWP) ≤15 mmHg on a previous right heart catheterization (RHC) of acceptable quality

      OR

    - In the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH *at screening*, as defined by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) (Peak tricuspid regurgitation velocity [TRV] ≥2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria (Galie et al. 2015)

In summary, the study consists of 5 phases:

- Run-in period of 12 weeks (if needed)
- Screening period
    - +/- 28-day washout period (if needed*); this can be part of the Run-in period if the Run-in period is applicable*
    - Screening period (up to 28 days). Patients will be evaluated for eligibility based on the inclusion and exclusion criteria
- Double-blind treatment period (52 weeks)
- Follow-up period (4 weeks)
- In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 ~~visit~~ for up to 12*1* months safety follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

Approximately 176 patients will be enrolled at approximately 75 study centers in Canada, Europe (EU) and Eastern Europe, Middle East, and Africa (EEMEA), *and potentially Asia-Pacific*. No replacements will be made.

In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 for up to 1*1* months safety follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

The study ends when all patients complete the *overall* 12 months safety follow-up described below*, i.e., 4 weeks follow-up after end of treatment at week 52 plus additional 11 months safety follow-up after the Follow-up visit at week 56.*

In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 ~~visit~~ for up to 1~~2~~*1* months safety follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

SECTION 3.3.2: RATIONALE FOR PATIENT POPULATION

In this study, patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH, will be studied. Overall, there is no robust information regarding the efficacy, tolerability and safety of the combination of sildenafil and pirfenidone in patients with IPF and there are currently no approved therapies for PH secondary to lung disease (Group 3 PH), including PH secondary to IPF.

SECTION 3.3.5: RATIONALE FOR BIOMARKER ASSESSMENTS

Certain biomarkers may be differentially expressed in patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH on pirfenidone treatment (e.g., possibly cytokines, chemokines and other cellular and molecular markers of lung injury and fibrosis).

SECTION 4.1: PATIENTS

Approximately 176 patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH, who have been on pirfenidone in a dose range of 1602 to 2403 mg/day with demonstrated tolerability will be enrolled in this study.

Key inclusion criteria for the study are presented in Figure 2 and the eligibility criterion for ~~intermediate or high probability~~ *risk* of Group 3 PH (Decision Tree) is further detailed in Figure 3.

SECTION 4.1.1: INCLUSION CRITERIA

6. For the purposes of this study patients have to present with:
   - advanced IPF is defined as a measurable DLCO ≤40% of predicted value at Screening;

   AND

   - ~~intermediate or high probability~~ *risk* of Group 3 PH*,* as defined by:
     - mPAP ≥20 mmHg together with PAWP ≤15 mmHg on a previous RHC of acceptable quality.

     OR

     - In the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH at screening, as defined by the 2015 ESC/ERS (peak TRV) ≥2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria (Galie et al 2015).

SECTION 4.1.2: EXCLUSION CRITERIA

17. Use of any of the following therapies within 28 days prior to Screening:
    - Use of any medications specifically prescribed for the treatment of PH (other than study drug) after the Washout Period and throughout the study, including but not limited to endothelin receptor antagonists, prostaglandins, guanylate cyclase ~~inhibitors~~ *stimulators* ~~such as~~ such as riociguat (see Section 4.5 of the Sildenafil SPC [Section 1.2.2]) and other phosphodiesterase inhibitors

Additional Exclusion Criteria Based on Sildenafil Reference Safety Information

6. Recent history of stroke or myocardial infarction,

~~7. Severe hypotension (BP <90/50 mmHg)~~

~~8.~~7. Known hereditary degenerative retinal disorders such as retinitis pigmentosa

~~9.~~8. Patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia)

~~10. Use of an alpha blocker~~

~~11.~~9. Patients with bleeding disorders or active peptic ulceration.

~~12.~~10. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

SECTION 4.4.2: PROHIBITED THERAPY

- Use of any medications specifically prescribed for the treatment of pulmonary hypertension (other than study drug) after the Washout Period and throughout the study, including but not limited to endothelin receptor antagonists, prostaglandins, guanylate cyclase ~~inhibitors~~ *stimulators* ~~such as~~ such as riociguat and other phosphodiesterase inhibitors

SECTION 4.5.5: LABORATORY, BIOMARKER, AND OTHER BIOLOGICAL SAMPLES

Blood and urine samples for hematology, biochemistry, biomarkers, urinalysis and pregnancy testing will be collected as per the Schedule of Assessments (see Appendix 1) and will be analyzed at a central laboratory *(exception local laboratory for countries with local requirements)*:

SECTION 4.5.16: PATIENT STUDY TREATMENT DISCONTINUATION

Patients must discontinue study treatment (sildenafil and/or pirfenidone) if they experience any of the following (see also Sections 5.1.1 and 5.1.2):

- Inability to tolerate study treatment after efforts have been made to gain tolerability
- An elevation in liver test results of the magnitude described below
- Use of a prohibited investigational therapy or concomitant medication
- Sildenafil/placebo will be stopped ~~in any patient with systolic blood pressure (SBP) <100 mmHg or diastolic blood pressure (DBP) <50 mmHg;~~ in patients with acute coronary syndromes, atrioventricular AV block, life-threatening arrhythmias, left ventricular dysfunction (ejection fraction <25%), or clinically significant visual changes
- Pregnancy
- Signs or symptoms of angioedema
- Any other treatment-emergent adverse event or toxicity that is unacceptable in the opinion of the patient or Investigator

Sildenafil/placebo will be stopped (temporarily or permanently) in any patient with systolic blood pressure (SBP) <100 mmHg or diastolic blood pressure (DBP) <50 mmHg.

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

~~The per protocol (PP) population is defined as all randomized patients who complete the 52-week treatment period without major protocol violations.~~

The safety population is defined as *all patients randomized, taking at least one dose of randomized Sildenafil/Placebo treatment.* ~~all treated patients (at least one drug intake of pirfenidone or sildenafil)~~. Patients in the safety population will be assigned to treatment groups according to the treatment they received.

SECTION 6.4.1: PRIMARY EFFICACY ENDPOINT

The primary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment in patients with advanced IPF and ~~intermediate or high probability~~ *risk* of Group 3 PH.

The primary analysis will be based on the ITT population, defined as all randomized patients. Patients who discontinue treatment prematurely will be analyzed based on the available data. No imputation method will be applied. Patients who undergo lung transplantation during the study will be withdrawn from the study at the time of hospitalization for transplantation. *In addition, sensitivity analysis of the primary endpoint will be performed. The details of those analyses will be provided in the Statistical Analysis Plan.* ~~As a sensitivity analysis, the analysis will be repeated based on the PP population, defined as all randomized patients who will complete the 52-week treatment regimen without major protocol violations.~~

SECTION 10: REFERENCES

F. Hoffmann La Roche Ltd. Investigator's Brochure RO220912 Esbriet (pirfenidone) ~~Eleventh version, July 2016~~ *current version and associated addendums.*

FIGURE 1: Study Schema

Footnote Text: ** After the completion of the treatment period (Visit 10) and 4 weeks safety follow-up, the possibility will be offered to the patients to receive pirfenidone within the study protocol up to 1~~2~~*1* months safety follow-up.

FIGURE 2: Key Inclusion Criteria for the Study

Figure has been revised to reflect the change in terminology.

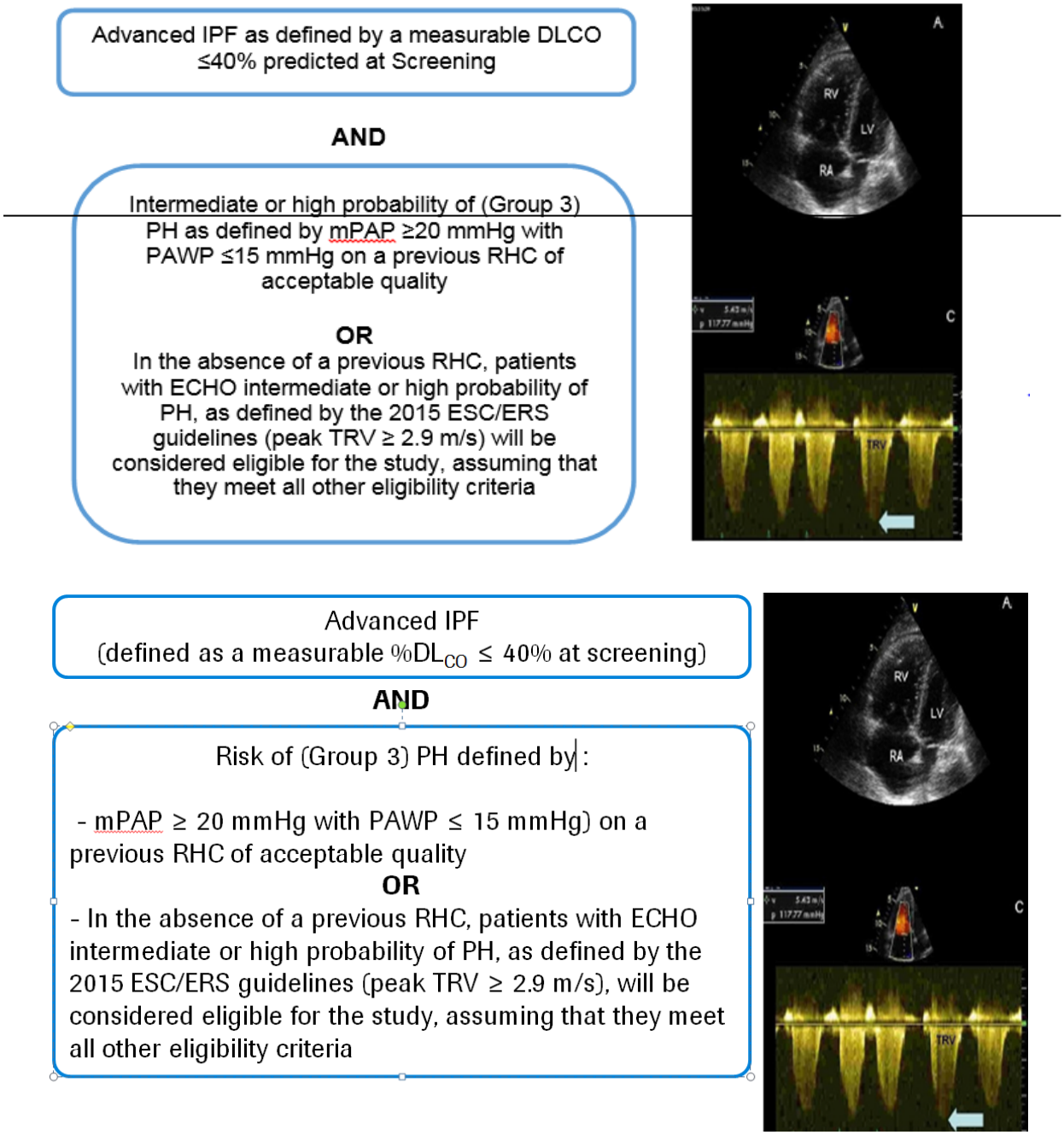

FIGURE 3: Eligibility Criterion for ~~Intermediate and High~~ *Risk* of Group 3 PH (Decision Tree)

Title of the figure has been updated to reflect the change in terminology

Appendix 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

Appendix 1
Schedule of Assessments

Day Week	Washout[a] -57 to -29	Screening[b] 28 to -1	Double blind treatment phase 1 W1	 22 W3	 45 W6	 90 W12	 135 W19	 180 W26	 225 W32	 270 W39	 315 W45	 365 W52	Early Study Withdrawal/ Study Treat. Discontinuation	Follow-Up (FU) 393	Additional safety FU[i] up to 12~~1~~ months
(Window, days)			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Informed Consent	X[c]														
Demographic data	X														
Medical History and Baseline Conditions	X	X													
Obtain and Review Historical PFTs, HRCT*, Surgical Lung Biopsy, and RHC		X													
Review Inclusion/Exclusion Criteria	X	X	X												
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight			X					X				X	X	X	
Height			X												
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Day Week	Washout[a] -57 to -29	Screening[b] 28 to -1	Double blind Treatment 1 W1	 22 W3	 45 W6	 90 W12	 135 W19	 180 W26	 225 W32	 270 W39	 315 W45	 365 W52	Early Study Withdrawal/ Study Treat. Discontinuation	Follow-Up 393	Additional safety FU [i,] up to 11 months
(Window, days)			**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**		**(±5)**	
Treatment Period Visit			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**Approx. every 3 months**
Spirometry post broncho-dilator (FVC, FEV1, FEV1/ FVC) [d]		X	X [d1]			X		X		X		X	X		
DLCO [e]		X	X [e1]			X		X		X		X	X		
6MWT and SpO_2 (resting, nadir, and end of test) [f]		X	X[f]		X	X		X		X		X	X		
Borg scale		X	X		X	X		X		X		X	X		
WHO Functional Class		X	X	X	X	X	X	X	X	X	X	X	X		
Hematology		X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry		X	X	X	X	X	X	X	X	X	X	X	X		
NT-proBNP, CRP, aldosterone			X			X		X				X	X		
Urinalysis		X	X			X		X				X	X		
Urine Pregnancy Test [g]			X	X	X	X	X	X	X	X	X	X	X		

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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PROTOCOL ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted] MD
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 your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SILDENAFIL ADDED TO PIRFENIDONE IN PATIENTS WITH ADVANCED IDIOPATHIC PULMONARY FIBROSIS AND *RISK* OF GROUP 3 PULMONARY HYPERTENSION**
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TEST PRODUCT:	Pirfenidone (RO0220912) and sildenafil (RO0280296)
PHASE:	Phase IIb
INDICATION:	Idiopathic pulmonary fibrosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and tolerability of sildenafil or placebo added to pirfenidone treatment (study treatments) in patients with advanced idiopathic pulmonary fibrosis (IPF) and *risk* of Group 3 pulmonary hypertension (PH) who are on a stable dose of pirfenidone with demonstrated tolerability. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment in patients with advanced IPF and *risk* of Group 3 PH. The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

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

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

  - Any decline >25% from baseline or
  - A decline between 15-25% from baseline, if accompanied by at least one of the following:
    - worsening of oxyhemoglobin (SpO2) desaturation during the 6-minute walk test (6MWT) compared to baseline
    - worsening of the maximum Borg scale during the 6MWT compared to baseline
    - Increased O_2 requirements during the 6MWT compared to baseline

Secondary Efficacy Objectives (Full details are given in Protocol Section 6.4.2)

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

- Progression-free survival (PFS), defined as the time to decline in 6MWD of ≥15% compared with baseline as defined above, respiratory-related non-elective hospitalization, or death from any cause
- Proportion of patients with decline in 6MWD of ≥15% from baseline as defined above
- Time to respiratory-related non-elective hospitalization
- Time to death from any cause
- Lung transplantation
- Time to all-cause non-elective hospitalization
- Time to respiratory-related death
- Change from baseline in transthoracic echocardiography (ECHO) parameters
- Change from baseline in pulmonary function tests (PFTs)
- Change from baseline in oxyhemoglobin saturation (SpO2) at rest and during the 6-minute walk test (6MWT)
- World Health Organization (WHO) Functional Class
- Dyspnea (assessed by the University of California San Diego Shortness of Breath Questionnaire – UCSD SOBQ)
- Health-related quality of life (HRQoL) (assessed by the Saint George's Respiratory Questionnaire [SGRQ])
- N-terminal pro-brain natriuretic peptide (NT-proBNP) level

SAFETY OBJECTIVE

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

- Nature, frequency, severity, relationship and timing of treatment-emergent adverse events
- Changes in vital signs
- Findings on physical examination
- Clinical laboratory test results
- 12-lead electrocardiograms (ECGs)
- Study discontinuation or study drug discontinuation

Study Design

Description of Study

This is a Phase IIb, randomized, placebo-controlled, multicenter, international study of the efficacy, safety, and tolerability of combination treatment with sildenafil and pirfenidone in patients with advanced IPF and *risk* of Group 3 PH who are on pirfenidone in a dose range of 1602 to 2403 mg/day with demonstrated tolerability. For the purposes of this study, patients have to present with:

- advanced IPF as defined by a measurable pulmonary diffusing capacity (carbon monoxide diffusing capacity [DLCO]) ≤40% of predicted value at Screening;

AND

- *risk* of Group 3 PH as defined by
  - mean pulmonary artery pressure (mPAP) ≥20 mmHg together with pulmonary artery wedge pressure (PAWP) ≤15 mmHg on a previous right heart catheterization (RHC) of acceptable quality

    OR
  - in the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH *at screening*, as defined by the 2015 European Society of

Cardiology/European Respiratory Society (ESC/ERS) (Peak tricuspid regurgitation velocity [TRV] ≥ 2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria (Galie et al. 2015)

Number of Patients

Approximately 176 patients will be enrolled at approximately 75 study centers in Canada, Europe (EU) and Eastern Europe, Middle East, and Africa (EEMEA), *and potentially Asia-Pacific*.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the study protocol in the opinion of the Investigator
- Age 40-80 years (inclusive) at Screening
- Diagnosis of IPF for at least 3 months prior to screening
- Confirmation of IPF diagnosis by the Investigator, in accordance with the 2011 international consensus guidelines (Raghu et al. 2011), at Screening
- Advanced IPF as defined by a measurable DLCO ≤40% of predicted value at Screening and *risk* of *Group* 3 PH (as previously defined in Study Design)
- Prior to the start of Screening, receiving pirfenidone for at least 12 weeks, and on a dose in the range of 1602 to 2403 mg/day for at least 4 weeks prior to the first Screening Visit. During this 4-week period, patients must not have experienced either a new or ongoing adverse event of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.03) Grade 2 or higher and considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment of >7 days for any reason. It is expected that the dose of pirfenidone will be in the range of 1602 to 2403 mg/day throughout the study (in countries where patients will not be able to take pirfenidone for 12 weeks due to reimbursement issues, this 12-week run-in supply will be provided by the Sponsor).
- WHO Functional Class II or III (Rubin 2004) at Screening
- 6MWD of 100 to 450 meters at Screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of <1% per year during the Treatment Period and for at least 58 days after the last dose of study treatment.
    - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal 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 non-hormonal 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, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men who are not surgically sterile: 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, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the Treatment Period and for at least 118 days after the last dose of study treatment. Men must refrain from donating sperm during this same period.

- With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 118 days after the last dose of study drug or study treatment to avoid exposing the embryo

Main Exclusion Criteria (Full details are given in Protocol Section 4.1.2)

Patients who meet any of the following Exclusion Criteria or additional Exclusion Criteria listed in the study Protocol will be excluded from study entry:

- History of any of the following types of PH: Group 1 (pulmonary arterial hypertension [PAH]); Group 1 (pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis); Group 2 (left-heart disease); Group 3 (due to conditions other than interstitial lung disease, including chronic obstructive pulmonary disease [COPD], sleep-disordered breathing, alveolar hypoventilation, high altitude, or developmental abnormalities); Group 4 (chronic thromboembolic pulmonary hypertension); Group 5 (other disorders) (Simonneau et al. 2013)
- History of clinically significant cardiac disease in the opinion of the Investigator, including, but not limited to: left ventricular ejection fraction <40%, congestive heart failure Class IV New York Heart Association (NYHA), left ventricular outflow obstruction (aortic stenosis, idiopathic hypertrophic subaortic stenosis), symptomatic coronary artery disease, congestive heart failure requiring hospitalization, second- or third-degree atrioventricular block, uncontrolled or clinically significant arrhythmias; uncontrolled systemic hypertension
- History of coexistent and clinically significant (in the opinion of the Investigator) COPD (including chronic bronchitis, emphysema), bronchiectasis, asthma, inadequately treated sleep-disordered breathing, or any clinically significant pulmonary diseases or disorders other than IPF or PH secondary to IPF
- Hypotension (blood pressure [BP] <100 mmHg systolic or <50 mmHg diastolic), autonomic dysfunction, or conditions in which vasodilation may cause an unsafe drop in BP
- History of use of drugs and toxins known to cause PAH, including aminorex, fenfluramine, dexenfluramine, and amphetamines. (For a full list see Galie et al, 2015)
- Initiating any new cardiac or pulmonary rehabilitation program within 28 days prior to Screening and throughout the study
- Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio <0.70 post bronchodilator at Screening
- Any impairment other than dyspnea that limits the patient's ability to walk for at least 6 minutes or perform other study procedures
- SpO2 saturation measured by pulse oximetry at rest <92% with ≥6 L of supplemental oxygen, at the first Screening Visit
- Significant clinical worsening of IPF between the first Screening Visit and Day 1, in the opinion of the Investigator
- Any serious medical condition, clinically significant abnormality on ECG at Screening or laboratory tests (hematology, serum chemistry, and urinalysis) that, in the opinion of the Investigator, may pose an additional risk in administering study treatment to the patient
- Clinical evidence of any active infection which according to the judgment of the Investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF
- Certain laboratory abnormalities or findings at Screening, including:
  - Total bilirubin above the upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × ULN
  - Alkaline phosphatase >2.0 × ULN
  - Creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault formula
- Pregnant or lactating, or intending to become pregnant during the study
- Extent of emphysema greater than the extent of fibrotic changes (honeycombing and reticular changes) on any previous HRCT scan, in the opinion of the Investigator

- Poorly controlled systemic hypertension (>180 mmHg systolic or >100 mmHg diastolic)
- Use of any of the following therapies within 28 days prior to Screening:
  - Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site
  - Any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambricentan, macitentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, corticosteroids (>15 mg/day prednisolone or equivalent more than 28 days), TNF-α inhibitors, imatinib mesylate, and interferon gamma-1b
  - Any medications that are specifically used for the treatment of IPF (other than the study drug) including those listed above. N-acetylcysteine (NAC) is acceptable, provided that the dose has been stable for 28 days prior to Screening and remains unchanged throughout the study
  - Use of any medications specifically prescribed for the treatment of PH (other than study drug) after the Washout Period and throughout the study, including but not limited to endothelin receptor antagonists, prostaglandins, guanylate cyclase *stimulators* such as riociguat (see Section 4.5 of the Sildenafil SPC [Section 1.2.2]) and other phosphodiesterase inhibitors
- Vasoactive medications including calcium channel blockers, diuretics, and vasodilators may not be added within 28 days prior to screening, and the dose of these medications must be held constant as much as possible within 7 days of Screening and throughout the study

End of Study

The end of the clinical trial is defined as the date when the last patient completes the last visit (LPLV) or the date at which the last data point which is required for the statistical analysis is received, whichever is the later date. LPLV for the primary analysis is expected to occur approximately 56 weeks after the last randomized patient begins the Treatment Period.

The study ends when all patients complete the *overall* 12 months safety follow up described below, *i.e., 4 weeks follow-up after end of treatment at week 52 plus additional 11 months safety follow-up after the Follow-up visit at week 56*.

Length of Study

For each patient the total length of the study is expected to be up to a maximum of approximately 64 weeks, including the Washout Period of 4 weeks, the Screening Period of up to 4 weeks, the Treatment Period of 52 weeks, and the Follow-up Period of 4 weeks.

In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 for up to 1*1* months safety follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

The test products for this study are pirfenidone and sildenafil.

Pirfenidone (5-methyl-1-phenyl-2-1(H)-pyridone) will be administered orally three times per day (TID) with meals, in a range of 1602 to 2403 mg/day. Each pirfenidone capsule contains 267 mg of pirfenidone. Pirfenidone (Esbriet®) will be supplied by the Sponsor as white, hard gelatin capsules printed with “267 mg” in brown ink.

Sildenafil 20 mg will be administered orally TID, about 4 to 6 h apart. Sildenafil will be supplied by the Sponsor as white, round, biconvex film-coated, tablets. Sildenafil tablets will by encapsulated by a compounding pharmacy to be identical in appearance and size to matching placebo.

Comparator

Placebo will be administered orally TID, about 4 to 6 h apart. Placebo will be supplied by the Sponsor as a capsule with the same appearance and size as the encapsulated sildenafil.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment on disease progression. The primary endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

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

  * Relevant decline in 6MWD from baseline is further specified as:

  - Any decline >25% from baseline or
  - A decline between 15-25% from baseline, if accompanied by at least one of the following:
    - worsening of SpO2 desaturation during the 6MWT compared to baseline
    - worsening of the maximum Borg scale during the 6MWT compared to baseline
    - increased O_2 requirements during the 6MWT compared to baseline.

The primary analysis will be based on the Intent-to-treat (ITT) population, defined as all randomized patients. Patients who discontinue treatment prematurely will be analyzed based on the available data. No imputation method will be applied. Patients who undergo lung transplantation during the study will be withdrawn from the study at the time of hospitalization for transplantation. *In addition, sensitivity analysis of the primary endpoint will be performed. The details of those sensitivity analyses will be provided in the Statistical Analysis Plan.* The primary analysis of the primary endpoint will compare disease progression rates in each treatment arm using a Chi-square test with a one-sided significance level $\alpha = 0.05$.

Determination of Sample Size

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

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

Interim Analyses

There are no planned interim efficacy analyses for this study. Safety interim analyses will be performed regularly by an independent Data Monitoring Committee (iDMC). Efficacy data will only be provided if requested by the iDMC. Further details on the function and logistics (e.g. frequency of the meetings) of the iDMC will be provided in the iDMC Charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALAT	Latin American Thoracic Society
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AV	atrioventricular
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
cGMP	cyclic guanosine monophosphate
CI	confidence interval
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CYP	cytochrome
DBP	diastolic blood pressure
DLCO	carbon monoxide diffusing capacity/ pulmonary diffusing capacity
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiography
eCRF	electronic Case Report Form
EDC	electronic data capture
EEMEA	Eastern Europe, Middle East, and Africa
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
ERK1/2	extracellular regulated kinases 1 and 2
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GAP	gender, age and physiology
GCP	Good Clinical Practice

GGT	gamma-glutamyl-transferase
GWAS	genome-wide association study
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health related quality of life
5-HT	serotonin
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IL	Interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IPF	idiopathic pulmonary fibrosis
IRB	independent review board
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
JRS	Japanese Respiratory Society
LDH	lactate dehydrogenase
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary artery pressure
6MWD	6-minute walk distance
6MWT	6-minute walk test
NAC	N-acetylcysteine
NAION	nonarteritic ischemic optic neuropathy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
PDE5	phosphodiesterase-5
PDGF	platelet-derived growth factor
PFS	progression-free survival
PFTs	pulmonary function tests
PH	pulmonary hypertension
PK	pharmacokinetics
PRO	patient reported outcome

PP	per-protocol
QD	Daily
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's formula
RBC	red blood cells
RHC	right heart catheterization
RNA	ribonucleic acid
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SGRQ	Saint George's Respiratory Questionnaire
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SPF	sun protection factor
SpO2	oxyhemoglobin saturation
TGF-β	transforming growth factor-beta
TID	three times daily
TRV	tricuspid regurgitation velocity
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
UV-A	ultraviolet A
UV-B	ultraviolet B
WBC	white blood cells
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON IDIOPATHIC PULMONARY FIBROSIS (IPF) AND ADVANCED IPF WITH PULMONARY HYPERTENSION

Idiopathic pulmonary fibrosis (IPF) is a devastating disease of unknown etiology characterized by fibrosis of the lung interstitium, decrease in lung volume and progressive pulmonary insufficiency typically leading to death (Lynch and Toews 1998). Idiopathic pulmonary fibrosis is a rare disease; recent prevalence estimates range from 14.0 to 63.0 per 100,000 in the United States (US) and from 1.25 to 23.4 per 100,000 in European Union (EU) (Raghu et al. 2006; Fernández Pérez et al. 2010; Nalysnyk et al. 2012). IPF is most prevalent in middle-aged and elderly patients, and most studies have found a higher frequency in men than in women (Nalysnyk et al. 2012).

Although the pathogenesis of IPF remains incompletely understood, the current view is that a series of microinjuries to the alveolar epithelium results in release of profibrotic mediators, causing fibroblast and myofibroblast proliferation, organization into fibroblastic foci, and excessive collagen deposition and accumulation (du Bois, 2010).

The initial clinical presentation of IPF is typically that of slowly progressive dyspnea and non-productive cough. Lung auscultation reveals fine end inspiratory crackles, initially at the base of the lung and ultimately diffusely (American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association [ATS/ERS/JRS/ALAT 2011]). In advanced disease, pulmonary hypertension (PH), which may lead to right heart failure often develops. Pulmonary function tests demonstrate a restrictive pattern, with a decrease in lung volumes and diffusing capacity for carbon monoxide (DLCO), and oxygen desaturation on exertion. Chest radiographs show diffuse interstitial opacities with volume loss, and high-resolution computed tomography (HRCT) scans show a characteristic pattern of peripheral (subpleural), bibasilar, reticular infiltrates, associated with architectural distortion, honeycomb changes and traction bronchiectasis (ATS/ERS/JRS/ALAT 2011). A diminished quality of life in patients with IPF is well established, with impaired energy level and decreased level of independence in concert with respiratory symptoms (Swigris et al. 2005; Tomioka et al. 2007).

To date, two approved IPF therapies are available: Esbriet® (pirfenidone) and Ofev® (nintedanib); both therapies have shown to significantly slow the progression of lung function decline in IPF, although the disease remains incurable. There are no approved therapies available for PH secondary to IPF.

1.2 BACKGROUND ON TEST PRODUCTS

The test products in this Phase IIb trial will be pirfenidone (Esbriet®) and sildenafil (generic formulation). Patients will have advanced IPF and *risk* of Group 3 PH, which is considered to be secondary to IPF, and be on a stable dose of pirfenidone with demonstrated tolerability.

1.2.1 Pirfenidone

Pirfenidone is an orally active, small molecule (molecular weight, 185.2 g/mol) antifibrotic agent, with anti-inflammatory properties. It has been approved for the treatment of IPF in the US, and is indicated in adults for the treatment of mild to moderate IPF in the EU and Canada. The recommended daily maintenance dose in patients with IPF is 2403 mg/day, administered as three 267 mg capsules (801 mg), three times daily (TID) with food, at the same times each day (Esbriet® EU Summary of Product Characteristics [SPC] and US label, 2014).

The broad antifibrotic activity of pirfenidone across organ systems has been demonstrated in more than 40 animal studies in models of fibrosis, including fibrosis of the liver, heart and kidney as well as several models of lung fibrosis (Schaefer et al. 2011). In bleomycin-induced pulmonary fibrosis models, pirfenidone reduced visible lung pathology, lung tissue hydroxyproline content, edema (wet-to-dry lung weight), and histologic score (Oku et al. 2008; PCLN-PIRF-009). Additionally, pirfenidone administration significantly suppressed bleomycin-induced increases in interleukin (IL)-1β, IL-6, monocyte chemoattractant protein-1, and IL-12p40 in these models.

In cell-based systems, pirfenidone suppressed the proliferation of fibroblasts; attenuated the production of profibrotic cytokines, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) from human macrophage cell lines; promoted release of collagenase from fibroblasts; and reduced the accumulation of extracellular matrix components, particularly collagen (Hirano et al. 2006; PCLN-PIRF-010).

Taken together, nonclinical studies conducted in vitro, as well as data derived from animal models of fibrosis, provide evidence that pirfenidone reduces levels of profibrotic growth factors and cytokines, lessens collagen deposition and reduces interstitial fibrosis; all physiological elements thought to be dysregulated in IPF.

Refer to the current version of the pirfenidone Investigator's Brochure for further details on nonclinical studies. (Esbriet [pirfenidone]).

Pirfenidone pharmacokinetics (PK) have been characterized in humans. After oral administration of a single dose of 801 mg (i.e., 1 of the 3 doses taken daily to reach the approved 2403 mg/day) in healthy, fed adults, pirfenidone is absorbed relatively slowly, with a mean peak plasma concentration of 7.87 µg/mL approximately 3 to 4 h after ingestion. The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and the maximum concentration (C_{max}) of pirfenidone when administered after a meal was significantly lower (using Food and Drug Administration [FDA] bioequivalence criteria) than when pirfenidone was given while fasting. A population PK analysis indicated that pirfenidone PK in IPF patients are similar to those in healthy subjects.

Clinical studies have shown pirfenidone is primarily metabolized by cytochrome (CYP) 1A2 with contribution from multiple other CYPs. The most clinically significant factors that can influence pirfenidone PK are moderate to severe hepatic impairment (moderate liver cirrhosis [Child-Pugh Class B]) and co-administration of moderate to strong CYP1A2 inhibitors or inducers (including smoking), detailed at the following website: http://www.medicine.iupui.edu/clinpharm/ddis/main-table/

Three randomized, double-blind, placebo-controlled Phase 3 studies evaluating pirfenidone in patients with IPF have been conducted: Studies PIPF-004 and PIPF-006, (CAPACITY) completed in 2008 (Noble et al. 2011) and Study PIPF-016 (ASCEND) completed in 2014 (King et al. 2014). Studies PIPF-004 and PIPF-006 evaluated the efficacy and safety of treatment with pirfenidone for a minimum of 72 weeks; the PIPF-016 evaluated treatment with pirfenidone for 52 weeks. A total of 1247 patients were included in the pooled Phase 3 analysis (Studies PIPF-004/006/016), of these 623 were randomized to treatment with pirfenidone (2403 mg/day) and 624 were randomized to treatment with placebo (Noble et al. 2015).

In the pooled Phase 3 analysis (Studies PIPF-004/006/016), there was a clear effect of treatment with pirfenidone in reducing the decline in percent predicted forced vital capacity (FVC) compared with placebo (the primary endpoint) ($p < 0.0001$, rank analysis of covariance [ANCOVA]). There was a relative reduction of 43.8% in the proportion of patients with a decline in percent predicted FVC ≥10% or death from Baseline at Month 12 in the pirfenidone group compared with the placebo group, as well as a 59.3% relative increase in the proportion with no decline in percent predicted FVC.

In the pooled Phase 3 analysis, key secondary endpoints showed a beneficial effect of pirfenidone on exercise tolerance, represented by a statistically significantly lower decline from baseline to Month 12 in the 6MWT in the pirfenidone group compared with the placebo group ($p = 0.0004$). There was also a 38% relative reduction in the risk of disease progression or death at Month 12 in pirfenidone-treated patients compared with placebo-treated patients (hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.51 – 0.75; $p < 0.0001$). In the mortality analysis, a 48% relative reduction in the risk of death from any cause favoring pirfenidone was seen (HR 0.52; 95% CI, 0.31 – 0.87; $p = 0.0107$, log-rank test). A smaller proportion of pirfenidone-treated patients died compared with placebo-treated patients (3.5% vs. 6.7%, respectively).

Safety outcomes were assessed in the three Phase 3 studies (Studies PIPF-004/006/016) and two ongoing open-label studies (002 and 012 [RECAP]), during the period from the first dose until 28 days after the last dose of study drug. A total of 1299 patients were included in the analysis. These findings represent a comprehensive analysis of safety outcomes in a large and well-defined cohort of 1299 patients with IPF treated with pirfenidone. During this long-term, prospective follow-up of up to 9.9 years, pirfenidone was safe and generally well tolerated. Gastrointestinal and skin-related events were among the most common adverse events (AEs) and were generally

mild-to-moderate in severity and responsive to dose modification. Elevations of aminotransferases typically occurred within the first 6 months of treatment and were generally transient, reversible with dose modification or discontinuation and without clinical sequelae (Lancaster et al. 2016).

Refer to the current version of the pirfenidone Investigator's Brochure (Esbriet [pirfenidone]) for further details on clinical studies.

1.2.2 Sildenafil

Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor. It has been approved as a 20 mg tablet (sildenafil citrate) for the treatment of pulmonary arterial hypertension in most countries worldwide, since 2005. The recommended daily maintenance dose is 20 mg TID, taken with or without food.

The inhibition of PDE5 by sildenafil enhances the vasodilatory effects of nitric oxide in PH by preventing the degradation of cyclic guanosine monophosphate (cGMP), which promotes relaxation of vascular smooth muscle and increases blood flow. In animal models and human trials, sildenafil has been found to produce a relatively selective reduction in pulmonary artery pressure (PAP) without adverse systemic hemodynamic effects (Ghofrani et al. 2002). Inhibition of PDE5 by sildenafil may also enhance the platelet antiaggregatory activity of nitric oxide and inhibit thrombus formation.

Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis) (Galie et al. 2015).

Refer to the SPC for sildenafil for further information at the following websites:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2582414d-0ef3-403e-84e8-1d6c812e7eb1

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000638/human_med_001033.jsp&mid=WC0b01ac058001d124

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

While drugs used to treat PH have either not been effective for treatment of IPF (bosentan, ambrisentan, macicentan) or are unlikely to be able to address the parenchymal changes in the fibrotic process, anti-fibrotic drugs are unlikely to have any

notable effect on the perfusion aspects of interstitial lung diseases (ILDs). Therefore, combination treatment appears as a promising approach to the major clinical problem of combined IPF and PH (Wuyts et al. 2014).

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

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

Milara at al. (2016) analyzed the role of sildenafil on vasoconstriction and remodeling of pulmonary arteries from patients with IPF and PH. Ex vivo pulmonary arteries from 18 donors without lung disease, nine IPF, eight PH+IPF and four PH patients were isolated to measure vasodilator and anti-contractile effects of sildenafil in an isometric organ bath. Ventilation/perfusion was explored in an animal model of bleomycin lung fibrosis. Sildenafil relaxed serotonin (5-HT) pre-contracted pulmonary arteries in healthy donors and IPF patients and, to a lesser extent, in patients with PH plus IPF, and PH. Sildenafil inhibited 5-HT dose-response contraction curve mainly in patients with PH and IPF, and PH, but not in healthy donors. Sildenafil did not impair the ventilation/perfusion mismatching induced by bleomycin. Pulmonary arteries from patients with PH plus IPF showed a marked expression of phosphodiesterse-5 and extracellular matrix components. Sildenafil inhibited pulmonary artery endothelial and smooth muscle cell to mesenchymal transition by inhibition of extracellular regulated kinases 1 and 2 (ERK1/2) and SMAD3 phosphorylation. These results suggest an absence of direct relaxant effect and a prominent anti-contractile and anti-remodeling role of sildenafil in PH plus IPF pulmonary arteries that could explain the beneficial effects of sildenafil in IPF patients with PH phenotype. A novelty and strength of this analysis relates to the direct study of sildenafil on contractile properties of pulmonary arteries obtained from patients with IPF with or without PH, and on markers of proliferation and mesenchymal cell transition. The

originality of the study is further strengthened by the finding of increased PDE5 expression in pulmonary arteries from patients with IPF with and without PH. It appears, that sildenafil has pleiotropic properties beyond its traditional vasodilatory effects that may render it especially attractive as an add-on treatment for IPF (Hassoun and Nathan 2016).

Previous clinical trials of sildenafil in IPF patients with PH have generally shown inconclusive results (Ghofrani et al. 2002, Collard et al. 2007, Jackson et al. 2010, IPFnet, 2010 [STEP-IPF]). This experience may be a consequence of several factors, including small sample size, short observation periods, imprecise definition of study populations, or selection of the primary endpoint. In the STEP-IPF randomized controlled trial, the effects of sildenafil were studied in a population of 180 patients with advanced IPF, defined as DLCO <35% of the predicted value. Although this study failed to meet its primary endpoint of ≥20% improvement in 6MWD, a number of secondary endpoints achieved statistical significance, including DLCO, dyspnea, oxygen saturation, and quality of life. Furthermore, in a subset of this population (119 patients) with echocardiograms available for post-hoc review, patients with right ventricular systolic dysfunction treated with sildenafil experienced a 99-meter lesser decline in 6MWD and improved quality of life compared with those who received placebo. (Han et al. 2013).

Recently, a study assessing the efficacy and safety of riociguat in patients with symptomatic PH associated with idiopathic interstitial pneumonias (IIP) (RISE-IIP) has been prematurely terminated (clinicaltrials.gov: NCT02138825) after the independent Data Monitoring Committee (iDMC) observed that patients receiving riociguat were at a possible increased risk for death and other serious adverse events (SAEs) compared with those receiving placebo.

In study MA29957, patients with advanced IPF and *risk* of Group 3 PH will be included. To address potential concerns regarding the RISE-IIP premature termination, but most importantly to minimize any potential risk in the study patient population in MA29957, a safety plan has been put in place for this study. The safety plan includes: appropriate eligibility criteria, dose modification and/or discontinuation guidelines for each identified and potential risk (see Section 5.1), *collecting from randomized patients the most recent HRCTs performed prior to entering the study*, monitoring of patients at risk as well as the regular monitoring of patient data by an iDMC. Moreover, the long-standing experience available with sildenafil should also be considered.

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety and tolerability of sildenafil compared to placebo added to pirfenidone treatment in patients with advanced IPF and *risk* of

Group 3 PH. The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

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

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

  - Any decline >25% from baseline or
  - A decline between 15-25% from baseline, if accompanied by at least one of the following:
    - worsening of SpO2 desaturation during the 6MWT compared to baseline
    - worsening of the maximum Borg scale during the 6MWT compared to baseline
    - increased O_2 requirements during the 6MWT compared to baseline.

Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of adding sildenafil compared with placebo, to pirfenidone treatment.	• Relevant decline in 6MWD of at least 15% from baseline (as defined below*), respiratory-related non-elective hospitalization, or all-cause mortality * Relevant decline in 6MWD from baseline is defined as: – Any decline >25% from baseline or – A decline between 15-25% from baseline, if accompanied by at least one of the following: o worsening of SpO2 desaturation during the 6MWT compared to baseline o worsening of the maximum Borg scale during the 6MWT compared to baseline o increased O_2 requirements during the 6MWT compared to baseline.
Secondary Efficacy Objectives: (see further details in Section 6.4.2)	
• The secondary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment.	• Progression-free survival (PFS), defined as time to decline in 6MWD of ≥15% compared with baseline as defined above, respiratory-related non-elective hospitalization, or death from any cause • Proportion of patients with decline in 6MWD of ≥15% from baseline as defined above • Time to respiratory-related non-elective hospitalization • Time to death from any cause • Lung transplantation • Time to all-cause non-elective hospitalization • Time to respiratory-related death • Change from baseline in transthoracic echocardiography (ECHO) parameters • Change from baseline in pulmonary function tests (PFTs) • Change from baseline in SpO_2 at rest and during the 6MWT • World Health Organization (WHO) Functional Class • Dyspnea (assessed by the UCSD SOGQ) • Health-related quality of life (HRQoL) (assessed by the Saint George's Respiratory Questionnaire [SGRQ]) • N-terminal pro-brain natriuretic peptide (NT-proBNP) level
Safety Objective:	
• The safety objective for this study is to evaluate the safety of adding sildenafil compared with placebo to pirfenidone treatment.	• Nature, frequency, severity, relationship and timing of treatment-emergent adverse events (TEAEs) • Changes in vital signs • Findings on physical examination • Clinical laboratory test results • 12-lead electrocardiograms (ECGs) • Study discontinuation or study drug discontinuation

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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

- advanced IPF as defined by a measurable DLCO ≤40% of predicted value at Screening;

AND

- *risk* of Group 3 PH as defined by
    - mean pulmonary artery pressure (mPAP) ≥20 mmHg together with pulmonary artery wedge pressure (PAWP) ≤15 mmHg on a previous right heart catheterization (RHC) of acceptable quality

    OR

    - In the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH *at screening*, as defined by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) (Peak tricuspid regurgitation velocity [TRV] ≥2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria (Galie et al. 2015)

After discussing the risks and benefits of the study with the Investigator and providing written informed consent, patients will be provided pirfenidone for the study by the Sponsor and will be instructed on proper use. Patients will be instructed to stop taking their commercial pirfenidone and start taking the study-provided pirfenidone.

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

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

After completing the Washout Period, patients will enter Screening. Patients not taking a prohibited medication will forgo the Washout Period and directly enter Screening.

In summary, the study consists of 5 phases:

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

At the start of Screening, patients will have been on oral pirfenidone taken TID for at least 12 weeks, and the dose will have been in the range of 1602 to 2403 mg/day, for at least 4 weeks prior to the first Screening Visit. It is expected that the dose will remain within the range of 1602 to 2403 mg/day throughout the study and in accordance with the product label. In addition, in the 4 weeks prior to the first Screening Visit, patients must not have experienced either a new or ongoing adverse event of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, which is Grade 2 or higher and considered, by the Investigator to be related to pirfenidone, or have had an interruption of pirfenidone treatment of >7 days for any reason.

During Screening, patients may return for the Baseline visit (Day 1) as soon as eligibility has been confirmed.

Patients who meet all eligibility criteria and who provide written, informed consent will be randomized 1:1 to receive 1 year (52 weeks) of treatment with either oral sildenafil (20 mg) or matching placebo TID while continuing to take pirfenidone. Treatment with sildenafil should be initiated and monitored by a physician experienced in the treatment of PAH.

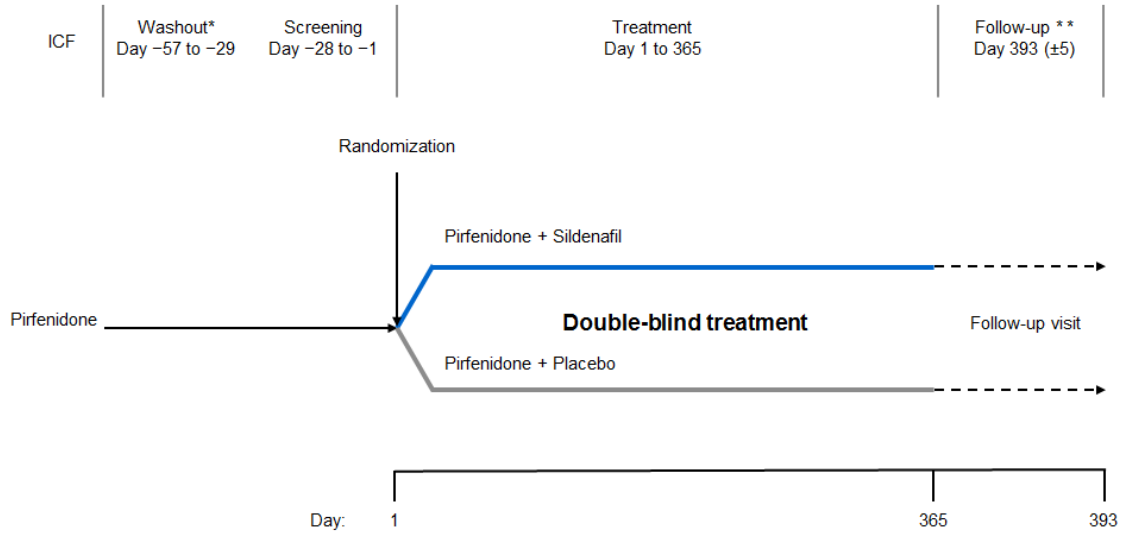
Approximately 176 patients will be enrolled at approximately 75 study centers in Canada, Europe (EU) and Eastern Europe, Middle East, and Africa (EEMEA), *and potentially Asia-Pacific*. No replacements will be made.

Patients who experience a primary endpoint (a decline in 6MWD as defined per protocol or an event of respiratory-related non-elective hospitalization) will continue treatment and be encouraged to complete the study.

The randomization will be stratified by previous RHC availability for inclusion (yes/no) and by degree of pulmonary function measured by forced expiratory volume in 1 second (FEV1)/FVC ratio below/above 0.8.

Patients will have a total of up to approximately 12 to 13 clinic visits, including one or more visits during the Washout and Screening Periods, up to 10 Treatment Period visits, and one Follow-up visit (see Figure 1).

Figure 1 Study Schema



ICF = Informed Consent Form

* Patients will be required to discontinue all prohibited medications and undergo a 28-day Washout Period prior to entering the study. Patients not taking a prohibited medication will directly enter Screening. A prior run-in period will be provided for countries where patients will not be able to take pirfenidone for 12 weeks due to reimbursement issues. The run-in period can include the Washout period (if applicable).
** After the completion of the treatment period (Visit 10) and 4 weeks safety follow-up, the possibility will be offered to the patients to receive pirfenidone within the study protocol up to 11 months safety follow-up.

In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 for up to 11 months safety

follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

A patient diary will be used to record adverse events, daily dosing adherence for both pirfenidone and sildenafil/placebo, and concomitant medication use from the Screening visit until the Follow-up visit. Also, patients will receive a wallet card that provides important information relevant to study participation.

During the study, assessments will be performed according to the Schedule of Assessments (Appendix 1).

An iDMC will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised. The iDMC may recommend that the Sponsor stop the study for safety concerns.

A detailed description of the procedures, data flow and the meeting schedule of the iDMC will be maintained in a separate iDMC Charter, by the Sponsor and the iDMC.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the clinical trial is defined as the date when the last patient completes the last visit (LPLV) or the date at which the last data point which is required for the statistical analysis is received, whichever is the later date. LPLV for the primary analysis is expected to occur approximately 56 weeks after the last randomized patient begins the Treatment Period.

The study ends when all patients complete the *overall* 12 months safety follow-up described below*, i.e. 4 weeks follow-up after end of treatment at week 52 plus additional 11 months safety follow-up after the Follow-up visit at week 56*.

The first patient is expected to enroll in the fourth quarter of 2016, and enrollment is anticipated to continue for approximately 15 months. The last patient is expected to complete the clinical trial approximately in the first quarter of 2019.

For each patient, the total length of the study is expected to be up to a maximum of approximately 64 weeks, including the Washout Period of 4 weeks, the Screening Period of up to 4 weeks, the Treatment Period of 52 weeks, and the Follow-up Period of 4 weeks. Patients who enter the 12-week run-in period will be included for a total length of 76 weeks.

In addition, the sponsor will offer the possibility to the patients to receive pirfenidone within the study protocol after the Follow-up visit at week 56 for up to 11 months safety follow-up. During this time, the patients should be evaluated by the treating physician approximately every three months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Pirfenidone and Sildenafil Doses and Schedule

In this study, sildenafil or placebo (as a comparator) will be added to ongoing treatment of a stable dose of pirfenidone. The doses will be in accordance with the prescribing information for both treatments: pirfenidone at the approved dose for IPF of 801 mg TID (or the stable dose they have entered into the study), taken at the same times each day with food, and sildenafil at the approved dose for pulmonary arterial hypertension (PAH) of 20 mg TID, with or without food.

Patients must have been on pirfenidone treatment for at least 12 weeks before the Screening visit and the dose must have been in the range of 1602 to 2403 mg/day with demonstrated tolerability for at least 4 weeks prior to the Screening Visit and throughout the study period.

The combination treatment will continue for 12 months in this study. Compared to a 6-month observation period (used in study STEP-IPF), 12 months will likely provide a greater number of primary events for the primary analysis, thus increasing the power of the study and the clinical validity, and also provide long-term safety data on the concomitant use of pirfenidone and sildenafil in this patient population.

All participants will be managed according to the best judgment of their treating physicians as informed by current local clinical practice guidelines and the best clinical evidence for patients with IPF and PH.

3.3.2 Rationale for Patient Population

In this study, patients with advanced IPF and *risk* of Group 3 PH, will be studied. Overall, there is no robust information regarding the efficacy, tolerability and safety of the combination of sildenafil and pirfenidone in patients with IPF and there are currently no approved therapies for PH secondary to lung disease (Group 3 PH), including PH secondary to IPF.

Clinical trials in IPF, including pirfenidone trials, have generally excluded patients with advanced disease and/or PH. Patients with PH secondary to advanced IPF therefore represent a group with high unmet medical need.

The expected benefits of the pirfenidone/sildenafil combination relate to the anticipated improvements in pulmonary hemodynamics in this patient population while the progression of fibrosis and decline in lung function are attenuated by pirfenidone.

3.3.3 Rationale for Control Group and Double-Blind Design

A double-blind, randomized trial design was identified to be the most appropriate design to allow for an unbiased evaluation of sildenafil taken with pirfenidone as a treatment for the study patient population. The analysis is focused on estimating the size of the

difference in the predefined outcomes between sildenafil co-administered with pirfenidone compared to placebo and pirfenidone. Patients are randomly allocated to treatment, and patients and Investigator (and other site personnel) remain unaware of which treatment is given.

3.3.4 Rationale for Primary Endpoint Selection

The primary endpoint in this double-blind, placebo controlled study will be a composite of exercise capacity (using the 6MWT), respiratory-related (non-elective) hospitalizations and all-cause mortality. This has been expanded from the primary endpoint of only using the 6MWT in most previous studies.

3.3.5 Rationale for Biomarker Assessments

Genomic, transcriptomic and proteomic profiling of markers associated with the molecular pathways and cellular processes of lung injury and fibrosis will be measured.

Certain biomarkers may be differentially expressed in patients with advanced IPF and *risk* of Group 3 PH on pirfenidone treatment (e.g., possibly cytokines, chemokines and other cellular and molecular markers of lung injury and fibrosis). The blood biomarker samples that are being obtained for this study may help identify those serum and plasma proteins or blood ribonucleic acid (RNA) biomarkers related to disease progression. See Schedule of Assessments (Appendix 1) for summary of serum, plasma and blood RNA biomarker study assessments.

Genetic polymorphisms have been demonstrated to alter the development and clinical course of a number of different diseases. The purpose of assessing genetic polymorphisms in this study is to understand their potential role in the pathogenesis and associated clinical outcomes. The assessment of genetic polymorphisms will only be conducted at institutions in which such research is in accordance with institutional regulations.

Patient participation for these assessments is voluntary and declining participation will in no way influence eligibility for this study. See Schedule of Assessments (Appendix 1) for summary of serum, plasma and blood deoxyribonucleic acid (DNA) biomarker study assessments.

3.3.6 Rationale for Choice of Stratification Factors

The randomization will be stratified by availability of a previous RHC (yes/no) and by FEV1/FVC ratio below/above 0.8, to ensure an equal distribution of patients with some degree of pulmonary obstruction in both treatment groups. Stratified randomization is included as the treatment outcome may be affected by these factors.

3.3.7 Rationale for Interim Analyses

An iDMC will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised. The iDMC may recommend

that the Sponsor stop the study for safety concerns. A detailed description of the procedures, data flow and the meeting schedule of the iDMC will be maintained in a separate iDMC Charter, by the Sponsor and the iDMC.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 176 patients with advanced IPF and *risk* of Group 3 PH, who have been on pirfenidone in a dose range of 1602 to 2403 mg/day with demonstrated tolerability will be enrolled in this study.

Key inclusion criteria for the study are presented in Figure 2 and the eligibility criterion for *risk* of Group 3 PH (Decision Tree) is further detailed in Figure 3.

Figure 2 Key Inclusion Criteria for the Study

- For the purposes of this study patients have to present with:

Advanced IPF
(defined as a measurable %DL_{CO} ≤ 40% at screening)

AND

Risk of (Group 3) PH defined by:

- mPAP ≥ 20 mmHg with PAWP ≤ 15 mmHg) on a previous RHC of acceptable quality

OR

- In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TRV ≥ 2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria

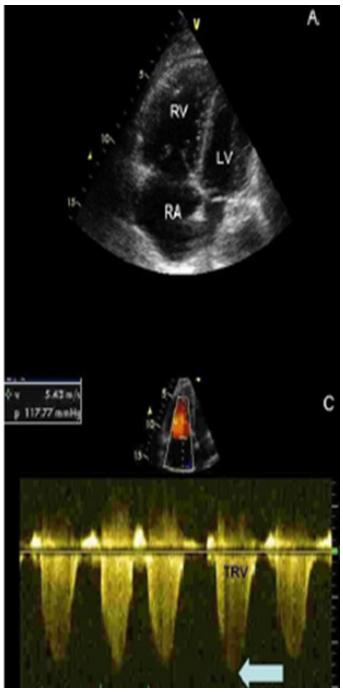
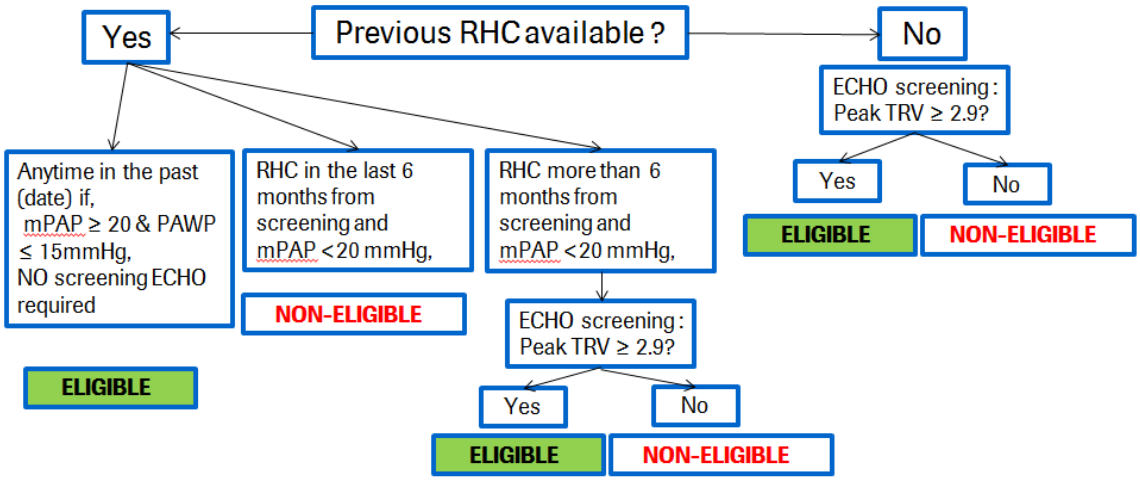


Figure 3 Eligibility Criterion for *Risk* of Group 3 PH (Decision Tree)



4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Ability to comply with the study protocol in the opinion of the Investigator
3. Age 40 to 80 years (inclusive) at Screening
4. Diagnosis of IPF for at least 3 months prior to Screening
5. Confirmation of IPF diagnosis by the Investigator, in accordance with the 2011 international consensus guidelines (Raghu et al. 2011), at Screening
6. For the purposes of this study patients have to present with:
   - advanced IPF is defined as a measurable DLCO ≤40% of predicted value at Screening;

   AND

   - *risk* of Group 3 PH as defined by:
     - mPAP ≥20 mmHg together with PAWP ≤15 mmHg on a previous RHC of acceptable quality.

     OR

     - In the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH at screening, as defined by the 2015 ESC/ERS (peak TRV) ≥2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria (Galie et al 2015).
7. Prior to the start of Screening, receiving pirfenidone for at least 12 weeks, at a dose in the range of 1602 to 2403 mg/day for at least 4 weeks prior to the first Screening Visit. During this 4-week period, patients must not have experienced either a new or ongoing adverse event of NCI CTCAE (version 4.03) Grade 2 or

higher and considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment of >7 days for any reason. It is expected that the dose of pirfenidone will be in the range of 1602 to 2403 mg/day throughout the study (in countries where patients will not be able to take pirfenidone for 12 weeks due to reimbursement issues, this 12-week run-in supply will be provided by the Sponsor)

8. WHO Functional Class II or III (Rubin 2004) at Screening
9. 6MWD of 100 to 450 meters at Screening
10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a non-hormonal contraceptive method with a failure rate of <1% per year during the Treatment Period and for at least 58 days after the last dose of study treatment
    - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal 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 non-hormonal 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, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
11. For men who are not surgically sterile: 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, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the Treatment Period and for at least 118 days after the last dose of study treatment. Men must refrain from donating sperm during this same period.
    - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 118 days after the last dose of study drug or study treatment to avoid exposing the embryo

4.1.2 Exclusion Criteria

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

1. History of any of the following types of PH: Group 1 (PAH); Group 1 (pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis); Group 2 (left-heart disease); Group 3 (due to conditions other than interstitial lung disease, including chronic obstructive pulmonary disease [COPD], sleep-disordered breathing, alveolar hypoventilation, high

altitude, or developmental abnormalities); Group 4 (chronic thromboembolic pulmonary hypertension); Group 5 (other disorders) (Simonneau et al. 2013)

2. History of clinically significant cardiac disease in the opinion of the Investigator, including, but not limited to: left ventricular ejection fraction <40%, congestive heart failure Class IV New York Heart Association (NYHA), left ventricular outflow obstruction (aortic stenosis, idiopathic hypertrophic subaortic stenosis), symptomatic coronary artery disease, congestive heart failure requiring hospitalization, second- or third-degree atrioventricular block, uncontrolled or clinically significant arrhythmias; uncontrolled systemic hypertension
3. History of coexistent and clinically significant (in the opinion of the Investigator) COPD (including chronic bronchitis, emphysema), bronchiectasis, asthma, inadequately treated sleep-disordered breathing, or any clinically significant pulmonary diseases or disorders other than IPF or PH secondary to IPF
4. Hypotension (blood pressure [BP] <100 mmHg systolic or <50 mmHg diastolic), autonomic dysfunction, or conditions in which vasodilation may cause an unsafe drop in blood pressure
5. History of use of drugs and toxins known to cause PAH, including aminorex, fenfluramine, dexenfluramine, and amphetamines. (For a full list see Galie et al, 2015)
6. Initiating any new cardiac or pulmonary rehabilitation program within 28 days prior to Screening and throughout the study
7. FEV1/FVC ratio <0.70 post bronchodilator at Screening
8. Any impairment other than dyspnea that limits the patient's ability to walk for at least 6 minutes or perform other study procedures
9. SpO2 saturation measured by pulse oximetry at rest <92% with ≥6 L of supplemental oxygen, at the first Screening Visit
10. Significant clinical worsening of IPF between the first Screening Visit and Day 1, in the opinion of the Investigator
11. Any serious medical condition, clinically significant abnormality on ECG at Screening or laboratory tests (hematology, serum chemistry, and urinalysis) that, in the opinion of the Investigator, may pose an additional risk in administering study treatment to the patient
12. Clinical evidence of any active infection which according to the judgment of the Investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF
13. Certain laboratory abnormalities or findings at Screening, including:
    - Total bilirubin above the upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × ULN
    - Alkaline phosphatase >2.0 × ULN
    - Creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault formula

14. Pregnant or lactating, or intending to become pregnant during the study
15. Extent of emphysema greater than the extent of fibrotic changes (honeycombing and reticular changes) on any previous HRCT scan, in the opinion of the Investigator
16. Poorly controlled systemic hypertension (>180 mmHg systolic or >100 mmHg diastolic)
17. Use of any of the following therapies within 28 days prior to Screening:
    - Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site
    - Any cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambricentan, macitentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, corticosteroids (>15mg/day prednisolone or equivalent more than 28 days) TNF-α inhibitors, imatinib mesylate, and interferon gamma-1b
    - Any medications that are specifically used for the treatment of IPF (other than the study drug) including those listed above. N-acetylcysteine (NAC) is acceptable, provided that the dose has been stable for 28 days prior to Screening and remains unchanged throughout the study
    - Use of any medications specifically prescribed for the treatment of PH (other than study drug) after the Washout Period and throughout the study, including but not limited to endothelin receptor antagonists, prostaglandins, guanylate cyclase *stimulators* such as riociguat (see Section 4.5 of the Sildenafil SPC [Section 1.2.2]) and other phosphodiesterase inhibitors
18. Vasoactive medications including calcium channel blockers, diuretics, and vasodilators may not be added within 28 days prior to screening, and the dose of these medications must be held constant as much as possible within 7 days of Screening and throughout the study
19. History of cancer likely to result in significant disability or to require medical or surgical intervention within the next 2 years. This does not include minor surgical procedures for localized skin cancer such as basal cell carcinoma.
20. Smoked tobacco within 3 months prior to Screening or is unwilling to avoid tobacco products (cigarettes, pipe, cigars) throughout the study
21. Illicit drug or significant alcohol abuse within 12 months prior to Screening, in the Investigator's judgment
22. Concomitant treatment with strong or moderate cytochrome P450 (CYP)1A2 inhibitors or moderate CYP1A2 inducers within 4 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment and throughout the study
    - Strong CYP1A2 inhibitors: fluvoxamine, enoxacin

- Moderate CYP1A2 inhibitors: ciprofloxacin (if dosed at >500 mg twice daily [BID]), mexiletene, thiabendazole, oral contraceptives, phenylpropanolamine, zileuton
- Moderate CYP1A2 inducers: montelukast, phenytoin, smoking
- Inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, erythromycin), or their inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort).

23. Hepatic impairment, acute or chronic hepatitis or known liver cirrhosis
24. Severe renal impairment including end-stage renal disease requiring dialysis
25. Poorly controlled diabetes mellitus requiring insulin therapy
26. Known HIV infection
27. ECG with a heart-rate–corrected QT interval (corrected using Fridericia's formula [QTcF]) ≥500 ms at Screening, or a family or personal history of long QT syndrome.

Additional Exclusion Criteria Based on Pirfenidone Reference Safety Information

1. Any contraindication to pirfenidone, including known hypersensitivity to the active substance or any excipient
2. Pirfenidone should not be used in patients with a history of angioedema due to pirfenidone
3. Concomitant use of fluvoxamine

Additional Exclusion Criteria Based on Sildenafil Reference Safety Information

1. Any contraindication to sildenafil, including known hypersensitivity to the active substance or any excipient;
2. Co-administration with nitric oxide donors (such as amyl nitrite) or organic nitrates (nitroglycerin) in any form (potentiates the hypotensive effects)
3. The co-administration of PDE5 inhibitors, including Viagra, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension
4. Combination with the most potent of the CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir)
5. A loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
6. Recent history of stroke or myocardial infarction
7. Known hereditary degenerative retinal disorders such as retinitis pigmentosa
8. Patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions

which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia)

9. Patients with bleeding disorders or active peptic ulceration.
10. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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

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

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

If unblinding is necessary for patient management (e.g., in the case of a SAE for which patient management might be affected by knowledge of treatment assignment), the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a SAE).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the Investigator or Sponsor to be related to study drug.

Unblinding should not necessarily result in the withdrawal of a patient from the study. Every effort should be made to retain unblinded patients in the study.

4.3 STUDY TREATMENT

The test products for this study (study treatments) are pirfenidone, blinded comparator sildenafil and a matching placebo to blinded comparator sildenafil.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Pirfenidone

Pirfenidone (Esbriet®), chemical name 5-methyl-1-phenyl-2-1(H)-pyridone, will be supplied by the Sponsor as white, hard gelatin capsules printed with “267 mg” in brown ink. Each pirfenidone capsule contains 267 mg of pirfenidone and the following inactive ingredients:

- Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate
- Capsule shell: gelatin, titanium dioxide, brown printing ink (includes shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide)

For information on the handling and storage of pirfenidone, see the current version of the pirfenidone Investigator's Brochure (Esbriet [pirfenidone]).

4.3.1.2 Sildenafil

Sildenafil will be supplied by the Sponsor as hard gelatin capsule (bovine only) containing a white, round, biconvex film-coated, commercial tablet Sildenafil 20mg from US market and microcrystalline cellulose as backfill. Each tablet contains sildenafil citrate United States Pharmacopeia (USP), equivalent to 20 mg sildenafil, and the following excipients:

- croscarmellose sodium; calcium phosphate, dibasic, anhydrous; magnesium stearate; cellulose, microcrystalline; polyethylene glycol 3350; polyethylene glycol 4000; polyvinyl alcohol; talc; titanium dioxide

For information of the sildenafil tablet, see the sildenafil SPC at the following website:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2582414d-0ef3-403e-84e8-1d6c812e7eb1

4.3.1.3 Placebo

Placebo will be supplied by the Sponsor as a capsule with the same appearance and size as the encapsulated sildenafil containing microcrystalline cellulose.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Pirfenidone

At the start of Screening, patients will have been taking pirfenidone, by oral administration, three times per day (TID) with meals for at least 12 weeks, and the dose must have been in the range of 1602 to 2403 mg/day for at least 4 weeks (prior to the first Screening Visit). Doses will be taken at the same time each day. It is expected that the dose will remain within the range of 1602 to 2403 mg/day throughout the study.

A patient diary will be used to record daily dosing adherence for pirfenidone.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.

Any overdose or incorrect administration of 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 study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Sildenafil or Placebo

Patients who meet all eligibility criteria and provide written informed consent will be randomized 1:1 to receive 1 year (52 weeks) of treatment with either oral sildenafil 20 mg or matching placebo TID, while continuing to take pirfenidone.

Daily dosing adherence for sildenafil or placebo will be recorded in the patient diary.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the adverse event eCRF.

4.3.2.3 Precautionary Measures during Treatment with Pirfenidone and/or Sildenafil

4.3.2.3.1 Pirfenidone

Exposure to sunlight (including indirect light, sunlamps, and tanning beds) should be avoided or minimized during pirfenidone treatment due to the possibility of photosensitivity reactions or rash. Patients should be instructed to use sunscreens that have a sun protection factor (SPF) ≥50 as well as protection against ultraviolet A (UV-A) and ultraviolet B (UV-B) radiation, and also to wear clothing that protects against sun exposure and avoid concomitant medications known to cause photosensitivity reactions, if possible.

All doses of pirfenidone are to be taken with food to reduce the likelihood of gastrointestinal symptoms.

Dose titration when pirfenidone is restarted after a treatment interruption is intended to enhance tolerability.

4.3.2.3.2 Sildenafil

Sildenafil may cause decreases in blood pressure due to vasodilator effects. Patients should be treated with caution if they have: resting hypotension (blood pressure [BP] <90/50 mmHg), hypertension (BP >170/110 mmHg), fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction, and also patients receiving

alpha blockers or other antihypertensive medication. Sildenafil is not recommended for use in patients with pulmonary veno-occlusive disease.

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Sildenafil should be used with caution in patients with cardiovascular disease, in patients receiving concurrent bosentan and in patients with bleeding disorders or with active peptic ulcer disease; as safety and efficacy have not been established.

Sildenafil should be used with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia). In the event of an erection that persists longer than 4 h, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Rare cases of NAION have been reported; risk may be increased with history of vision loss. In the event of any sudden visual defect, the treatment should be stopped immediately and alternative treatment should be considered.

Sildenafil may cause dose-related impairment of color discrimination and should be used with caution in patients with retinitis pigmentosa.

Cases of sudden decrease in hearing and hearing loss with the use of PDE5 inhibitors such as sildenafil have been reported.

Orthostatic hypotension has occurred rarely in patients receiving sildenafil (<2%).

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil should be administered to these patients only after careful benefit-risk assessment.

In PAH patients, there may be a potential for increased risk of bleeding when sildenafil is initiated inpatients already using a Vitamin K antagonist, particularly in patients with PAH secondary to connective tissue disease.

4.3.2.4 Missed Doses

If a patient misses a scheduled dose of pirfenidone and/or sildenafil, the dose should be skipped. Regular dosing will resume with the next scheduled dose. The patient should not take any extra doses to make up for missed doses.

4.3.2.5 Dose Modification or Discontinuation

The Investigator will be responsible for monitoring patients as frequently as clinically indicated for treatment-emergent adverse events or other toxicities, and for doing so in a manner consistent with the instructions in the labels for pirfenidone, sildenafil, and any other medications used to treat a study patient. The Investigator may contact the Medical Monitor or designee to discuss dose modification or discontinuation of study treatment. All treatment-emergent adverse events and toxicities will be followed according to procedures in this protocol. If a patient experiences a clinically significant treatment-emergent adverse event or toxicity, treatment of symptoms and/or temporary dose reduction, interruption, or discontinuation of study treatment should be considered. All changes in dosing will be recorded by the patient in the patient diary and by the study center in the electronic eCRF.

If a patient is hospitalized for any reason, the Investigator should consider continuing the study treatment if appropriate. If the patient is hospitalized at an institution that is not affiliated with the study center, the Investigator is encouraged to discuss study participation with the treating physician at the earliest possible time. All records pertaining to the hospitalization should be obtained by the study center. The Investigator will be responsible for determining the reason for hospitalization (admission to the hospital) (respiratory, cardiac, other), distinguishing elective from non-elective hospitalization, and determining the cause of death (respiratory, cardiac, other). The sections below identify events that require interruption/discontinuation of study treatment, and provide guidance for modifying doses, restarting treatment after an interruption.

4.3.2.6 Restarting Study Treatment

After a treatment interruption, study treatment can be restarted, at the discretion of the Investigator. The schedule for pirfenidone re-titration according to the label, is described in Table 2.

Table 2 Schedule for Pirfenidone Re-titration After an Interruption of More Than 14 Consecutive Days

Day (relative to restart of pirfenidone treatment)	Pirfenidone dosage (as tolerated)
Days 1 to 7	1 capsule TID, with food
Days 8 to 14	2 capsules TID, with food
Day 15 onwards	3 capsules TID, with food

TID = three times daily

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (pirfenidone, sildenafil and placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) 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.

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.

4.3.4 Continued access of Pirfenidone

The sponsor will offer the possibility to the patient to receive pirfenidone within the study protocol for 12 months safety FU after completing visit 10.

Following this period, the Sponsor will offer post-trial access to pirfenidone free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for advanced IPF and PH or suspected PH
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for advanced IPF and PH or suspected PH

- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

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 28 days prior to initiation of study drug to the study completion/ discontinuation visit. A patient diary will be used to record concomitant medications. All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All medical therapies necessary to treat the patient's comorbidities and which are not listed below in Section 4.4.2 are permitted in this study.

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

Sildenafil and PDE5 inhibitors that are used only intermittently for erectile dysfunction are permitted in the 28 days before the start of Screening but not after Screening and the remainder of the study. PDE5 inhibitors other than sildenafil used intermittently for erectile dysfunction are not allowed throughout the study.

Small steroid doses (e.g., 15 mg prednisolone or equivalent) are acceptable during the study. N-acetylcysteine is also acceptable during the study.

Corticosteroids may be used at the discretion of the investigator, without dose restriction, for a period of up to 28 days in patients experiencing an episode of acute IPF exacerbation. The study drug should be continued during this time, if possible.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study treatment:

- 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, high dose of corticosteroids (>15mg/day prednisolone or equivalent for more than 28 days), mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, TNF-α inhibitors, imatinib mesylate, Interferon gamma-1b and tyrosine kinase inhibitors

- Strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin), inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin), or their inducers (e.g., rifampicin, carbamazepine, phenytoin, phenytoin, St John's wort)
- Medications that are specifically being used for the treatment of IPF, including but not limited to angiotensin converting enzyme inhibitors, colchicine, heparin, warfarin, 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
- Use of any medications specifically prescribed for the treatment of pulmonary hypertension (other than study drug) after the Washout Period and throughout the study, including but not limited to endothelin receptor antagonists, prostaglandins, guanylate cyclase *stimulators* such as riociguat and other phosphodiesterase inhibitors
- Any investigational therapy in a clinical study
- Because moderate inhibitors of CYP1A2 (e.g., ciprofloxacin) increase systemic exposure of pirfenidone (Esbriet® US label 2014), if ciprofloxacin is administered it should be limited to 250 or 500 mg daily (QD), and the patient should be monitored close
- Nitric oxide donors (such as amyl nitrite) or nitrates in any form due to the hypotensive effects of nitrates

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 or CYP3A4. 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

The consumption of grapefruit juice will be prohibited during the study.

4.4.4 Additional Restrictions

The use of any tobacco product will be prohibited during the study.

4.5 STUDY ASSESSMENTS

The Procedure Manual and Laboratory Manual, referenced below is for specific study assessments, are documents that are separate from the protocol. These manuals will include full details of how to perform the procedure or assessment and will be available at each site.

Please see Appendix 1 for the Schedule of Assessments 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.

Separate informed consent needs to be given to allow for biomarker analyses.

All Screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria 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.

Screening assessments must take place within 28 days prior to baseline, this may comprise 1 or more visits for the convenience of the patient.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, 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 before the Screening period will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (as allowed by local regulations).

4.5.3 Physical Examinations

Physical examinations will be conducted as per the schedule of assessment (see Appendix 1). The directed physical examination should be based on signs and symptoms of the patient. Physicians should pay particular attention to the signs and symptoms that are characteristic of IPF and PH. Additional physical examinations may be performed only if clinically indicated. Physical examinations will include weight (kg); in addition, at Baseline, the examination will include height (cm) and body mass index (BMI) will be calculated. If clinically significant abnormalities are observed in a physical examination the Investigator will decide if they are new adverse events.

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

4.5.4 Vital Signs

Vital signs will include measurements of:

- Respiratory rate
- Heart rate
- Systolic and diastolic blood pressure while the patient is in a seated position, after at least 5 minutes rest and
- Temperature.

Vital signs should be measured at Screening and at each subsequent visit (as shown in Appendix 1).

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Blood and urine samples for hematology, biochemistry, biomarkers, urinalysis and pregnancy testing will be collected as per the Schedule of Assessments (see Appendix 1) and will be analyzed at a central laboratory *(exception local laboratory for countries with local requirements)*:

- Hematology (hemoglobin, hematocrit, red blood cells [RBC], platelet count, white blood cells [WBC] with differential [including neutrophils, lymphocytes, monocytes, eosinophils and basophils])
- Serum chemistry (glucose, blood urea nitrogen [BUN], creatinine, sodium, potassium, bicarbonate, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], AST, ALT, gamma-glutamyl-transferase [GGT]), C-reactive protein [CRP] and NT-proBNP, aldosterone)
- Optional: Serum and plasma collected at Screening and baseline visits for protein IPF biomarker measurements
- Optional: Blood PAXgene collected at Screening and baseline visits for transcriptomic IPF biomarker measurements
- Optional: Blood for DNA collected at baseline visit for genetic IPF biomarker measurements, which may include a genome-wide association study (GWAS)
- Urinalysis (dipstick including pH, specific gravity, glucose, protein, ketones, blood, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Pregnancy test: All women of childbearing potential will have serum and urine pregnancy tests as per the Schedule of Assessments (see Appendix 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual for this study.

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.

Biomarker samples will be destroyed 5 years after the end of the study.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.6 WHO Functional Class

World Health Organization Functional Class for PH must be documented at Screening (and be in the range 2 to 3) and re-assessed during the study, as outlined in the Schedule of Assessments (see Appendix 1).

The WHO Functional Class will be performed according to standard guidelines.

4.5.7 GAP Score and Index for IPF

The gender, age and physiology (GAP) score and index for IPF will be automatically calculated based on the information recorded in the eCRF (age, gender, FVC and DLCO).

4.5.8 12-lead Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1).

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.

Patients must have been in a supine or semi-supine position for at least 5 minutes prior to the recording being taken. 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. 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.

Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The ECG printout must be (1) reviewed by a medically qualified member of the study team at the site, (2) annotated to indicate any clinical finding and (3) dated and signed by this person and filed in the patient notes. ECG parameters will be entered into the eCRF.

If any ECG abnormality is associated with an adverse event, it must be recorded as described in Section 5.2.1.

4.5.9 6-Minute Walk Test and Oxyhemoglobin Saturation

The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. Oxyhemoglobin saturation (SpO_2) at rest and during the 6MWT will be assessed at specified timepoints, as outlined in the Schedule of Assessments

(see Appendix 1). The 6MWT will be performed according to standard procedures (ATS Statement, 2002) described in the Procedure Manual.

The 6MWT will be performed once for the visits highlighted in the Schedule of Assessments (Appendix 1). At Day 1, 6MWT will be performed twice and the better of the two 6MWT values will be reported as the baseline value. It is important to remember that for each 6MWT, information on oxyhemoglobin desaturation, Borg scale and O_2 requirements have to be collected.

4.5.10 Transthoracic Doppler ECHO

Transthoracic Doppler ECHO will be assessed at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1).

The ECHO procedure will be performed according to standard guidelines (Galiè et al. 2015).

4.5.11 Spirometry (Post bronchodilator)

Spirometry assessments of FVC, FEV1, and FEV1/FVC ratio will be assessed at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1).

Spirometry will be performed only post bronchodilator, approximately 30 minutes after the last puff of short-acting bronchodilator as described in the Procedure Manual. Reference equations for spirometric indices will also be provided in the Procedure Manual.

4.5.12 Diffusing Capacity for Carbon Monoxide

DLCO will be assessed at specified timepoints, as outlined in the Schedule of Assessments (see Appendix 1).

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

4.5.13 Health Status and Health-Related Quality of Life

HRQoL will be assessed by SGRQ at selected clinical visits as outlined in the Schedule of Assessments (see Appendix 1).

4.5.14 UCSD SOBQ

The UCSD SOBQ is a symptom-specific, 24-item, patient-self-administered questionnaire that assesses shortness of breath while doing a variety of activities of daily living. It will be assessed at selected clinical visits as outlined in the Schedule of Assessments (see Appendix 1).

4.5.15 Patient Study 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 study at any time. 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
- Lung transplantation
- Investigator or Sponsor determines it is in the best interest of the patient

Every attempt should be made to keep patients on study treatment throughout the duration of the trial.

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.

The Investigator should show due diligence and explore all possible options to reach a patient who fails to attend a visit. The site must document all attempts to contact the patient in the medical records / source documents.

4.5.16 Patient Study Treatment Discontinuation

Patients must discontinue study treatment (sildenafil and/or pirfenidone) if they experience any of the following (see also Sections 5.1.1 and 5.1.2):

- Inability to tolerate study treatment after efforts have been made to gain tolerability
- An elevation in liver test results of the magnitude described below
- Use of a prohibited investigational therapy or concomitant medication
- Sildenafil/placebo will be stopped in patients with acute coronary syndromes, atrioventricular AV block, life-threatening arrhythmias, left ventricular dysfunction (ejection fraction <25%), or clinically significant visual changes
- Pregnancy
- Signs or symptoms of angioedema
- Any other treatment-emergent adverse event or toxicity that is unacceptable in the opinion of the patient or Investigator

Sildenafil/placebo will be stopped (temporarily or permanently) in any patient with systolic blood pressure (SBP) <100 mmHg or diastolic blood pressure (DBP) <50 mmHg.

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

4.5.17 Study and Site 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 studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

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

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 and sildenafil are both approved treatments and all safety information is contained in their respective EU SPCs and US prescribing information. For this study, the Reference Safety Information (RSI) for pirfenidone is the Investigator Brochure (I.B.). For this study, the Reference Safety Information (RSI) for sildenafil is the US Prescribing Information.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2582414d-0ef3-403e-84e8-1d6c812e7eb1

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. Safety-related interim analyses will be performed, including hospitalizations and all-cause mortality, and the data assessed by the iDMC (see Section 3.1). All procedures are detailed in the Schedule of Assessments (Appendix 1).

5.1.1 Risks Associated with Pirfenidone

5.1.1.1 Impaired Hepatic Function

Elevations in ALT and AST >3 × ULN have been reported in patients receiving therapy with pirfenidone. These have rarely been associated with concomitant elevations in bilirubin. Liver function tests (ALT, AST and bilirubin) will be conducted at Screening and Day 1 prior to the initiation of study treatment and subsequently at each clinic visit during the study. In the event of significant elevation of liver aminotransferases, the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed in Table 3.

Table 3 Management of Dosing in Patients with Elevated Aminotransferase Test Results

Management or Elevation in ALT or AST	Recommendation
> 3 to < 5 × ULN without hyperbilirubinemia	Discontinue confounding medications Monitor the patient closely, including repeat liver chemistry tests. Maintain the daily dose at full dose, if clinically appropriate, or reduce or interrupt the dose (e.g., until liver chemistry test results are within normal limits) with subsequent re-titration to full dose as tolerated.
> 3 to < 5 × ULN with symptoms or hyperbilirubinemia	Discontinue pirfenidone and the patient should not be rechallenged
> 5 × ULN	Discontinue pirfenidone and the patients should not be rechallenged.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

5.1.1.2 Photosensitivity Reaction and Rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with pirfenidone. Patients should be instructed to use an effective 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 Investigator. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash.

5.1.1.3 Gastrointestinal Effects

In clinical trials, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported by patients in the pirfenidone treatment groups than in those taking placebo (see Esbriet [pirfenidone], current version of the Investigator's Brochure). Dose reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the pirfenidone 2403 mg/day group discontinued treatment due to a

gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dose reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dose modifications may be necessary in some cases of gastrointestinal adverse reactions. Taking pirfenidone with food is recommended.

The incidence of gastrointestinal events was higher early in the course of treatment (with highest incidence occurring during the initial 3 months) and usually decreased over time.

5.1.1.4 Angioedema

Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of pirfenidone in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of pirfenidone should immediately discontinue treatment and should be managed according to standard of care. Pirfenidone should not be used in patients with a history of angioedema due to pirfenidone.

5.1.1.5 Dizziness

Dizziness has been reported in patients taking pirfenidone. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination. If dizziness does not improve or if it worsens in severity, dose adjustment or even discontinuation of pirfenidone may be warranted.

5.1.1.6 Fatigue

Fatigue has been reported in patients taking pirfenidone. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring physical or mental activity.

5.1.1.7 Weight Loss

Weight loss has been reported in patients treated with pirfenidone. Physicians should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.

5.1.2 Risks Associated with Sildenafil

The main risks associated with sildenafil are given below. A complete list of risks associated with sildenafil is provided in the label:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2582414d-0ef3-403e-84e8-1d6c812e7eb1

5.1.2.1 Vasodilatory Action

When prescribing sildenafil, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by sildenafil's mild to moderate

vasodilatory effects, for example patients with hypotension, patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction.

5.1.2.2 Cardiovascular Risk Factors

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors.

5.1.2.3 Visual Events

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. In the event of any sudden visual defect, the treatment should be stopped immediately and alternative treatment should be considered.

5.1.2.4 Vitamin K Antagonists

In PAH patients, there may be a potential for increased risk of bleeding when sildenafil is initiated in patients already using a Vitamin K antagonist, particularly in patients with PAH secondary to connective tissue disease.

5.1.2.5 Veno and Vaso-occlusive Disease

No data are available with sildenafil in patients with PH associated with pulmonary veno-occlusive disease. However, cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Consequently, should signs of pulmonary edema occur when sildenafil is administered in patients with PH, the possibility of associated veno-occlusive disease should be considered.

Sildenafil should not be used in patients with PH secondary to sickle cell anemia. In a clinical study events of vaso-occlusive crises requiring hospitalization were reported more commonly by patients receiving sildenafil than those receiving placebo leading to the premature termination of this study.

5.1.2.6 Priapism

Sildenafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than 4 h, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

5.1.2.7 Alpha Blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker as the co-administration may lead to symptomatic hypotension in susceptible individuals. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment.

Physicians should advise patients what to do in the event of postural hypotensive symptoms.

5.1.2.8 Bleeding Disorders

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil should be administered to these patients only after careful benefit-risk assessment.

5.1.2.9 Galactose intolerance

Lactose monohydrate is present in the tablet film coat. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

5.1.2.10 Use of Sildenafil with Bosentan

The efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated.

5.1.2.11 Concomitant Use with Other PDE5 Inhibitors

The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitor products, including Viagra, has not been studied in PAH patients and such concomitant use is not recommended.

5.1.3 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in the labels for pirfenidone and sildenafil.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of review of the patient diary for adverse events, dosing adherence and concomitant medications, 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 (GCP), 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 as described in Section 5.3.5.9
- 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)

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 5.3.5.10)
- 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

- 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 NCI CTCAE version 4.03; 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 h 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)

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 h 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.

5.3 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 Section 5.4 to Section 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 all adverse events should be reported (see Section 5.4.2 for instructions for reporting serious adverse events) until 28 days after the last dose of study drug. 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?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (version 4.03) 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 (version 4.03), 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:

- 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

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

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, asterixis, 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. Details regarding any increases (or decreases) in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 h 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 h 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 advanced IPF and PH or suspected PH.

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 h after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 h 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 advanced IPF and PH, "advanced IPF" or "advanced PH" or "suspected IPF progression" or "suspected PH 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 Lack of Efficacy or Worsening of Advanced IPF and PH

Medical occurrences or symptoms of deterioration that are anticipated as part of advanced IPF and PH should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of advanced IPF and worsening of PH on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., " worsening of IPF" or "exacerbation of IPF" and "worsening of PH").

5.3.5.10 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
- 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

5.3.5.11 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 h after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from patient reported outcome (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 h after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 h 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 the events above to the Sponsor immediately (i.e., no more than 24 h 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 independent review board/ethics committee (IRB/EC).

5.4.1 Emergency Medical Contacts

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 h 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 all adverse events 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 h 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. Investigators should record all case details that can be gathered immediately (i.e., within 24 h 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 from 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 h 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 post-study adverse events 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 12 weeks 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 h 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 drugs 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 118 days (17 weeks) 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 h 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 h 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 h 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, 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 document{s}:

- Pirfenidone Investigator's Brochure
- US Prescribing information (USPI) for Sildenafil

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in the ITT population will be assigned to treatment groups as randomized.

The safety population is defined as *all patients randomized, taking at least one dose of randomized Sildenafil/Placebo treatment.* Patients in the safety population will be assigned to treatment groups according to the treatment they received.

The primary analysis of the study will be conducted when all patients completed the 52 weeks treatment phase and the mandatory 4 weeks Follow-up visit.

6.1 DETERMINATION OF SAMPLE SIZE

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

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

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, duration of follow up, discontinuation from the study, and reasons for discontinuation will be summarized by treatment arm for all randomized patients. In addition, major protocol violations will be summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics, such as age, sex, and race, will be summarized by treatment arms using means or medians for continuous variables and proportions for categorical variables. Medical history will be tabulated by treatment arms. Summary of concomitant medications will be displayed by treatment arms in frequency tables.

6.4 EFFICACY ANALYSES

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

6.4.1 Primary Efficacy Endpoint

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

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

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

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

    - Any decline >25% from baseline or
    - A decline between 15-25% from baseline, if accompanied by at least one of the following:
      - worsening of SpO2 desaturation during the 6MWT compared to baseline

- worsening of the maximum Borg scale during the 6MWT compared to baseline
- increased O_2 requirements during the 6MWT compared to baseline.

The primary analysis will be based on the ITT population, defined as all randomized patients. Patients who discontinue treatment prematurely will be analyzed based on the available data. No imputation method will be applied. Patients who undergo lung transplantation during the study will be withdrawn from the study at the time of hospitalization for transplantation. *In addition, sensitivity analysis of the primary endpoint will be performed. The details of those analyses will be provided in the Statistical Analysis Plan.*

The primary analysis of the primary endpoint will compare disease progression rates in each treatment arm using a Chi-square test with a one-sided significance level $\alpha = 0.05$.

6.4.2 Secondary Efficacy Endpoints

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

- Progression-free survival, defined as time to decline in 6MWD of ≥15% compared with baseline (as defined above), respiratory-related non-elective hospitalization, or death from any cause will be analyzed using Kaplan-Meier techniques and the two treatment arms will be compared with a log-rank test. In addition, hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models.
- The proportion of patients with decline in 6MWD of ≥15% from baseline (as defined above), will be compared using a Chi-square test with a one-sided significance level $\alpha=0.05$. The change in 6MWD from baseline to 12 months will be analyzed using a rank ANCOVA model with the 6MWD recorded at 12 months as the outcome variable and standardized rank baseline 6MWD as a covariate.
- Respiratory-related non-elective hospitalization, all-cause mortality, all-cause non-elective hospitalization and respiratory-related mortality will be analyzed using Kaplan-Meier techniques and the two treatment arms will be compared with a log-rank test. In addition, hazard ratios and corresponding 95% CI will be calculated by applying Cox-proportional hazard models.
- Changes from Baseline to End of Treatment for the following ECHO parameters:
  - Peak tricuspid regurgitation velocity (m/s)
  - PAPs

Pulmonary function tests (PFTs), i.e., FVC, FEV1, FEV1/FVC, and DLCO will be analyzed in terms of absolute mean changes from baseline to week 52 of treatment in actual and % of predicted values. In addition, 5% and 10% categorical changes from baseline will be summarized descriptively. The change from baseline for all

aforementioned parameters will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.

- Oxyhemoglobin saturation (SpO2) at rest and during the 6MWD will be summarized descriptively over time.
- Borg scale measurement of perceived exertion will be summarized descriptively over time.
- Lung transplantation will be analyzed descriptively.
- WHO Functional Class will be summarized descriptively over time.
- Dyspnea as assessed by the UCSD SOBQ will be summarized descriptively over time. The change from baseline will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.
- HRQoL assessed by SGRQ will be summarized descriptively over time. The change from baseline will be compared between the treatment arms using a rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate.
- Changes from baseline in in NT-proBNP levels will be summarized descriptively over time.

For all secondary endpoints p-values will be reported in a descriptive fashion. No multiplicity adjustments for statistical testing will be done.

6.4.3 Exploratory Efficacy Endpoints

The following subgroups will be included in this study for primary and selected secondary and efficacy endpoints: stratification factors (patients with RHC available at baseline and post bronchodilator FEV1/FVC ratio below/above 0.8), younger versus elderly, gender, etc.

Details of subgroup analyses will be given in the Statistical Analysis Plan (SAP).

All biomarker analyses will be of exploratory nature and be descriptive only.

6.5 SAFETY ANALYSES

The safety objective for this study is to evaluate the safety of adding sildenafil compared with placebo to pirfenidone treatment on the basis of the following analyses. The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed by adverse events, adverse events of Grade ≥3, serious adverse events, related adverse events, death, adverse events leading to study drug discontinuation or interruption, exposure to study medication, premature withdrawal from

the study (including reasons [especially withdrawal of consent]) and from the study medication, laboratory parameters, ECG and vital signs and summarized by treatment arms. Adverse events and cause of death will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events and serious adverse events will be summarized by primary system organ class and preferred term. Laboratory parameters, vital signs and ECG parameters will be presented descriptively over time and change from baseline will be reported. Findings on physical examinations will be summarized descriptively. The number and percentage of withdrawals from study medication or discontinuation from study together with the reasons will be summarized descriptively. The time from randomization until discontinuation will be displayed graphically using Kaplan-Meier techniques.

No formal statistical testing will be performed for safety parameters.

Data collected in the safety follow-up (i.e., adverse event and deaths) will be analyzed descriptively.

6.6 INTERIM ANALYSIS

There are no planned interim efficacy analyses for this study.

Safety interim analyses will be performed regularly by an iDMC. Efficacy data will only be provided if requested by the iDMC.

Further details on the function and logistics (e.g. frequency of meetings) of the iDMC will be provided in the iDMC Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

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

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

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(s) 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 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 7.5.

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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO 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, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the European Union or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form will be provided to each site. If applicable, 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 or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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.

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.

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 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, patients' medical records, and eCRFs. The Investigator will

permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The study will be overseen by a study management team of the Sponsor consisting of a clinical study manager, experienced medical staff (International Medical Director), statistician, and data management and quality assurance personnel.

Study monitoring, including data collection (source verification), site initiation and visits and adverse event processing (Medical Monitor) will be conducted by the Sponsor. The management of the database will also be performed by the Sponsor.

The study will be conducted under the leadership of an Executive Steering Committee. The Executive Steering Committee is composed of experts in IPF and PH and non-voting members representing Roche. The Executive Committee, together with the Sponsor, developed the study protocol and has overall responsibility for the study conduct and publication.

A separate Steering Committee Charter describing roles and responsibilities of the members of this committee will be maintained by the Sponsor.

The safety of the study will be monitored by the iDMC consisting of clinicians and statisticians experienced in conduct and safety review of controlled clinical studies. The iDMC will perform interim analyses for safety and, if needed review further safety data and give recommendation to the Sponsor. The study will be conducted using IxRS and a central laboratory provider.

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 website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. 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 Assessments

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

Appendix 1
Schedule of Assessments (cont.)

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

Appendix 1
Schedule of Assessments (cont.)

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

Appendix 1
Schedule of Assessments (cont.)

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

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

Appendix 1
Schedule of Assessments (cont.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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