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Clinical Trial Paper

Sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: A Phase IIb, randomised, double-blind, placebo-controlled study – Rationale and study design

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ABSTRACT

Background: Pulmonary hypertension (PH) is commonly observed in patients with advanced idiopathic pulmonary fibrosis (IPF). Despite the availability of therapies for both IPF and PH, none are approved for PH treatment in the context of significant pulmonary disease. This study will investigate the use of sildenafil added to pirfenidone in patients with advanced IPF and risk of PH, who represent a group with a high unmet medical need.

Methods: This Phase IIb, randomised, double-blind, placebo-controlled trial is actively enrolling patients and will study the efficacy, safety and tolerability of sildenafil or placebo in patients with advanced IPF and intermediate or high probability of Group 3 PH who are receiving a stable dose of pirfenidone. Patients with advanced IPF (diffusing capacity for carbon monoxide ≤40% predicted) and risk of Group 3 PH (defined as mean pulmonary arterial pressure ≥20 mm Hg with pulmonary arterial wedge pressure ≤15 mm Hg on a previous right-heart catheterisation [RHC], or intermediate/high probability of Group 3 PH as defined by the 2015 European Society of Cardiology/European Respiratory Society guidelines) are eligible. In the absence of a previous RHC, patients with an echocardiogram showing a peak tricuspid valve regurgitation velocity ≥2.9 m/s can enrol if all other criteria are met. The primary efficacy endpoint is the proportion of patients with disease progression over a 52-week treatment period. Safety will be evaluated descriptively.

Discussion: Combination treatment with sildenafil and pirfenidone may warrant investigation of the treatment of patients with advanced IPF and pulmonary vascular involvement leading to PH.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive and often rapidly fatal fibrosing interstitial lung disease with a 5-year survival rate between 20% and 40% [1,2], which is lower than that reported for many common cancers [2,3]. IPF profoundly affects patients' quality of life (QoL), with dyspnoea reducing physical functioning, leading to limited independence and depression [4,5]. Pirfenidone is an oral antifibrotic agent that slows IPF disease progression and, along with nintedanib, is one of only two antifibrotic therapies that were conditionally recommended for the treatment of IPF in the 2015 update to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society IPF treatment guidelines [6]. In addition, pirfenidone significantly reduces the decline in 6-minute walk distance (6MWD), which is a measure of an individual's functional status and ability to undertake activities of daily living [7,8], and significantly reduces the risk of death from any cause up to 120 weeks [9].

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Pulmonary hypertension (PH) is often found in patients with advanced IPF, and its occurrence increases with IPF disease severity. The incidence and prevalence of PH in patients with IPF remain unclear and estimates vary widely, from 8.1% to 84%, reflecting the heterogeneous subpopulations of patients studied, underlying disease severity, disease definition and different diagnostic measures used [10–14]. PH is a malignant prognostic determinant in patients with IPF, associated with a three-fold increase in mortality, especially when systolic pulmonary arterial pressure (sPAP) by echocardiogram (ECHO) exceeds 50 mm Hg [11,15,16]. The development of PH in patients with underlying IPF is also associated with a diminished exercise tolerance and QoL.

Although several targeted treatments are available for Group 1 (pulmonary arterial hypertension [PAH]) and Group 4 (chronic thromboembolic PH and other pulmonary artery obstructions [Table 1] [17]) PH, there are currently no approved therapies for PH in the context of significant pulmonary disease (Group 3), including PH in the context of IPF [17]. Indeed, therapies approved to treat PH have not been effective at targeting the underlying fibrotic parenchymal changes that occur in IPF [18–21], and the use of PH drugs in patients with IPF is not supported by evidence from randomised clinical trials.

Previous studies investigating the use of PAH drugs, including bosentan, ambrisentan, macitentan and riociguat, in patients with IPF have yielded inconsistent results, which may be due to differences in patient populations and experimental design [18–22]. Additionally, Phase II and III clinical trials in IPF, including the pirfenidone trials [23,24], have generally excluded patients with advanced IPF and/or PH. Nevertheless, it is unlikely that approved antifibrotics would have a notable effect on the vascular abnormalities that occur in patients with interstitial lung disease. Therefore, patients with PH in the context of IPF represent a group with a high unmet medical need.

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor that stabilises cyclic guanine monophosphate (cGMP), the secondary messenger for the pulmonary vasodilator nitric oxide (NO), and is approved for the treatment of PAH [25], but not PH in the context of significant pulmonary disease. In addition, sildenafil may confer survival benefits in paediatric patients with PAH [26,27] and improve haemodynamics in patients with thalassemia at risk of PH [28].

Results of previous clinical trials of sildenafil in PH in the context of IPF have generally been inconclusive, possibly owing to their small sample sizes, short observation periods, imprecise definitions of study populations or primary endpoint selection [29–34]. In the STEP-IPF trial, sildenafil was studied in a cohort of 180 patients with advanced IPF (defined as diffusing capacity for carbon monoxide [DLco] < 35% predicted) who were expected to have a high prevalence of PH. Although the primary endpoint of ≥20% improvement in 6MWD was not met, effects on secondary endpoints, such as DLco, dyspnoea, oxyhaemoglobin saturation (SaO_2) and QoL, achieved statistical significance [32]. In a substudy of STEP-IPF, patients with right ventricular systolic dysfunction experienced a significant 99-m lesser decline in 6MWD and improved QoL when treated with sildenafil compared with placebo [33]. Importantly, previous clinical trials of sildenafil in patients with IPF have not revealed any safety signals [32].

The beneficial effects of sildenafil on oxygenation and QoL parameters render it an attractive therapy for use in patients with IPF, particularly in the context of background antifibrotic therapy. Indeed, evidence from a small case-control study of 17 patients with progressive IPF suggested that sildenafil and pirfenidone may be administered safely in combination and may be associated with preserved DLco, setting a precedent for further controlled clinical trials investigating combination treatment with these two drugs [35].

The present study will evaluate the efficacy, safety and tolerability of sildenafil or placebo added to pirfenidone in patients with advanced IPF and intermediate or high probability of Group 3 PH who are receiving a stable dose of pirfenidone with demonstrated tolerability.

2. Materials and methods

2.1. Study design

This Phase IIb, randomised, placebo-controlled, multicentre, international study will investigate the efficacy, safety and tolerability of sildenafil or placebo in patients with advanced IPF and intermediate or high probability of Group 3 PH who are receiving pirfenidone (1602–2403 mg/day) with demonstrated tolerability. For this, patients should have received pirfenidone for at least 12 weeks, with no interruption or significant adverse events (AEs) due to pirfenidone in the last 28 days prior to screening.

The study will consist of five phases (Fig. 1; Table 2). First, a run-in period of 12 weeks will be provided for countries where patients will not otherwise be able to receive pirfenidone due to reimbursement restrictions. Second, a screening period of up to 28 days will be preceded by a 28-day washout period in patients receiving a prohibited medication; patients not receiving a prohibited medication will directly enter screening. In the 4 weeks prior to the screening visit, patients must not have experienced a new or ongoing AE of Grade 2 [36] or higher that is considered by the investigator to be related to pirfenidone, or have a > 7-day interruption of pirfenidone for any reason. Third, a 52-week, double-blind treatment period, including 10 visits, will form the main part of the study. After the treatment period, patients will continue to receive pirfenidone during the fourth phase, a safety follow-up of 4 weeks. During the fifth phase, an additional 12-month safety period after study visit 10, patients will be offered the possibility of continued access to pirfenidone, with evaluation approximately every 3 months. Patients will not continue to receive sildenafil after the 52-week, double-blind treatment period.

Patients who meet all eligibility criteria and provide written, informed consent will be randomised 1:1 by an interactive web-based response system to receive either oral pirfenidone plus oral sildenafil or oral pirfenidone plus matched placebo. Randomisation will be stratified by the availability of a previous right-heart catheterisation ([RHC] yes/no) and by a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio (below/above 0.8) to ensure an equal distribution of patients with some degree of pulmonary obstruction in both treatment groups. Pirfenidone will be administered three times daily, at the same times each day, and is expected to remain within the dose range of 1602 to 2403 mg/day throughout the study. Patients will also receive sildenafil 20 mg, or matched placebo, three times daily, in accordance with the approved dose for PAH; treatment with sildenafil will be monitored by a physician experienced in the treatment of PH. Daily dosing adherence for study medication will be recorded in the patient diary.

2.2. Patient population

At screening, patients will be aged 40 to 80 years, have a diagnosis of IPF for at least 3 months that is confirmed by the investigator and in line with the 2011 International Consensus Guidelines (2011) [37], be of World Health Organization functional class II or III and have a 6MWD of 100 to 450 m (Table 3). For this study, patients must present with advanced IPF defined by a measurable DLco ≤ 40% predicted at screening AND risk of Group 3 PH, defined as mean pulmonary arterial pressure (mPAP) ≥ 20 mm Hg with pulmonary artery wedge pressure ≤ 15 mm Hg on a previous RHC OR intermediate/high probability of Group 3 PH as defined by the 2015 European Society of Cardiology (ESC)/ERS guidelines (Fig. 2) [17]. In the absence of a previous RHC, patients with an ECHO showing a peak tricuspid valve regurgitation velocity (TRV) ≥ 2.9 m/s will be considered eligible, assuming all other criteria are met. A DLco of ≤ 40% predicted at screening was selected to define advanced IPF based on evidence that this threshold is associated with an increased risk of mortality [37], provide overlap with previous pirfenidone clinical studies and, when combined with RHC/ECHO inclusion criterion, increase the likelihood of including patients with

Table 1
Clinical classification of pulmonary hypertension (adapted from Ref. [17]).

Group 1: Pulmonary arterial hypertension	**Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia**
1.1 Idiopathic	3.1 Chronic obstructive pulmonary disease
1.2 Heritable	3.2 Interstitial lung disease
1.2.1 BMPR2 mutation	3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
1.2.2 Other mutations	3.4 Sleep-disordered breathing
1.3 Drugs and toxins induced	3.5 Alveolar hypoventilation disorders
1.4 Associated with:	3.6 Chronic exposure to high altitude
1.4.1 Connective tissue disease	3.7 Developmental lung diseases
1.4.2 HIV infection	
1.4.3 Portal hypertension	
1.4.4 Congenital heart disease	
1.4.5 Schistosomiasis	
Group 1: Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	**Group 4: Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions**
1.1 Idiopathic	4.1 Chronic thromboembolic pulmonary hypertension
1.2 Heritable	4.2 Other pulmonary artery obstructions
1.2.1 EIF2AK4 mutation	4.2.1 Angiosarcoma
1.2.2 Other mutations	4.2.2 Other intravascular tumours
1.3 Drugs, toxins and radiation induced	4.2.3 Arteritis
1.4 Associated with:	4.2.4 Congenital pulmonary artery stenosis
1.4.1 Connective tissue disease	4.2.5 Parasites (hydatidosis)
1.4.2 HIV infection	
Group 1: Persistent pulmonary hypertension of the newborn	**Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms**
Group 2: Pulmonary hypertension due to left heart disease	5.1 Haematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
2.1 Left ventricular systolic dysfunction	5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
2.2 Left ventricular diastolic dysfunction	5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
2.3 Valvular disease	5.4 Others: pulmonary tumoural thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	
2.5 Congenital/acquired pulmonary vein stenosis	

BMPR2 bone morphogenetic protein receptor type 2; *EIF2AK4* eukaryotic translation initiation factor 2 alpha kinase 4; *HIV* human immunodeficiency virus.

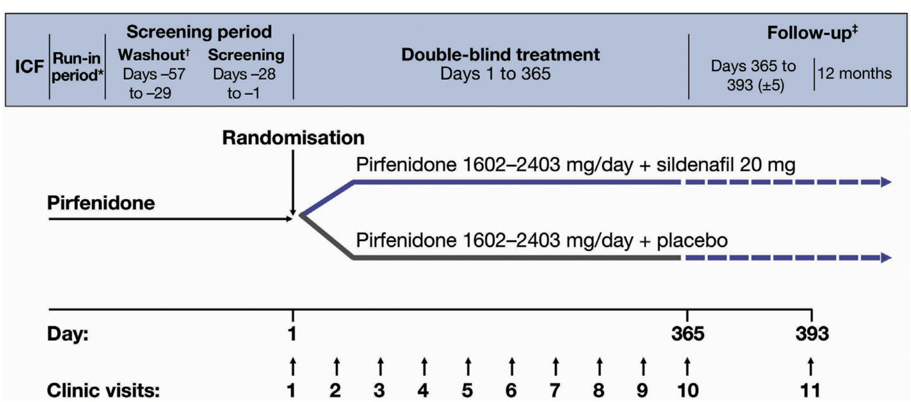

Fig. 1. Study design schematic.
ICF informed consent form.
* A prior run-in period will be provided for countries where patients will not be able to receive pirfenidone for 12 weeks due to reimbursement issues. The run-in period can include the washout period (if applicable).
† Patients will be required 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.
‡ After the completion of the treatment period (visit 10), patients will be offered the possibility of receiving pirfenidone within the study protocol for up to 12 months' safety follow-up.

pulmonary vasculopathy and a risk of PH. An mPAP ≥20 mm Hg was selected as an inclusion criterion as there is evidence that borderline PH is associated with increased mortality [33,38].

Patients with a history of PH that is not in the context of significant pulmonary disease (Group 3 [Table 1]) will be excluded from the study. Other exclusion criteria include a history of clinically significant cardiac and/or pulmonary disease (other than IPF or Group 3 PH), hypotension, FEV_1/FVC ratio < 0.70 post-bronchodilator, extent of emphysema greater than the extent of fibrotic changes (honeycombing and reticular changes) on any previous high-resolution computed tomography scan in the opinion of the investigator or history of drug and toxin use known to cause PAH. In addition, patients will be excluded if they meet the exclusion criteria based on pirfenidone and sildenafil reference safety information. Key inclusion and exclusion criteria are provided in Table 3.

Table 2
Summary of study phases.

Phase	Duration
Run-in period (if needed)	12 weeks (for patients who will not otherwise be able to receive pirfenidone due to reimbursement restrictions)
Screening period	± 28-day washout period Screening period (up to 28 days); evaluation of patients based on inclusion and exclusion criteria
Double-blind treatment period	52 weeks, 10 visits (1:1 pirfenidone plus oral sildenafil or oral pirfenidone plus matched placebo)
Follow-up period	4 weeks (continue to receive pirfenidone)
Safety follow-up	12 months from visit 10 (continue to receive pirfenidone)

Low steroid doses (15 mg prednisolone or equivalent) and N-acetylcysteine are permitted throughout the study period. In addition, corticosteroids may be used at the discretion of the investigator, without dose restriction, for up to 28 days in patients experiencing an acute exacerbation. During the study period, the use of the following drugs is prohibited: cytotoxic, immunosuppressive, cytokine-modulating or receptor-antagonist agents; the strong cytochrome (CYP) 1A2 inhibitors fluvoxamine and enoxacin; P-glycoprotein inhibitors or inducers; any medications used specifically for the treatment of IPF or PH (other than the study drugs), including but not limited to endothelin (ET) receptor antagonists, prostaglandins, guanylyl cyclase stimulators such as riociguat and other PDE-5 inhibitors; and NO donors.

Table 3
Key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
•Diagnosis of IPF for ≥3 months prior to screening •Investigator-confirmed IPF at screening consistent with the 2011 guidelines [37] •Advanced IPF, as defined as measurable DLco ≥40% predicted •Intermediate or high probability of Group 3 PH •Received pirfenidone for ≥12 weeks at 1602–2403 mg/day ≥4 weeks prior to screening, without any new or ongoing Grade 2 or higher adverse events (NCI CTCAE version 4.03) considered by the investigator as related to pirfenidone, or an interruption of pirfenidone for > 7 days for any reason •WHO functional class II or III [37,56] •6MWD 100–450 m •For women of childbearing potential and for men who are not surgically sterile, agreement to remain abstinent or to use contraception measures	•History of PH other than Group 3 PH due to interstitial lung disease •History of clinically significant cardiac and/or pulmonary disease (other than IPF or Group 3 PH) •History of drug or toxin use known to cause PAH, including aminorex, fenfluramine, dexfenfluramine and amphetamines •FEV_1/FVC ratio < 0.70 post-bronchodilator •SpO_2 at rest < 92% with ≥6 L supplemental oxygen •Extent of emphysema greater than extent of fibrotic changes on any previous HRCT scan, in the opinion of the investigator •Smoking tobacco in the previous 3 months, or illicit drug or significant alcohol abuse •ECG with heart rate–corrected QT interval (corrected to Fridericia's formula) ≥500 ms at screening, or family or personal history of long QT syndrome •Exclusion criteria based on pirfenidone or sildenafil reference safety information

6MWD 6-minute walk distance; *DLco* diffusing capacity for carbon monoxide; *ECG* electrocardiogram; *FEV_1* forced expiratory volume in 1 s; *FVC* forced vital capacity; *HRCT* high-resolution computed tomography; *IPF* idiopathic pulmonary fibrosis; *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events; *PAH* pulmonary arterial hypertension; *PH* pulmonary hypertension; *SpO_2* oxyhaemoglobin saturation; *WHO* World Health Organization.

2.3. Study objectives

This study will evaluate the efficacy, safety and tolerability of sildenafil compared with placebo when added to pirfenidone in the study population. The primary efficacy endpoint will be the proportion of patients showing disease progression over a 52-week treatment period, as evidenced by reaching the composite endpoint of relative decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalisations or all-cause mortality. A relative decline in 6MWD from baseline is further specified as any decline > 25% from baseline, or a decline between 15% and 25% from baseline if accompanied by at least one of the following: worsening of SpO_2 desaturation during the 6-minute walk test (6MWT) compared with baseline; worsening of the maximum Borg scale during the 6MWT compared with baseline; and increased O_2 requirements during the 6MWT compared with baseline. The composite primary endpoint has been expanded from the primary endpoint of the 6MWT used previously in this patient population and in clinical trials of PAH [30–32,39]. The 15% to 25% decline in the 6MWT utilised secondary criteria to avoid having patients return to the site to do a repeat 6MWD as occurred in the Phase III studies of pirfenidone to confirm a > 10% absolute change in % predicted FVC or 50-m decline in 6MWD.

The secondary efficacy objective for this study will further evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone on each of the individual components of the primary endpoint, as well as other parameters, as described in Table 4. The safety objective for this study will be to evaluate the safety of adding sildenafil compared with placebo to pirfenidone, and will be assessed by the nature, frequency, severity, relationship and timing of treatment-emergent AEs, changes in vital signs, findings on physical examination, 12-lead electrocardiogram (ECG) and study drug discontinuation (Table 4).

2.4. Safety considerations

Due to the potential risk of developing photosensitivity reaction/rash with pirfenidone, patients will be advised to avoid/minimise

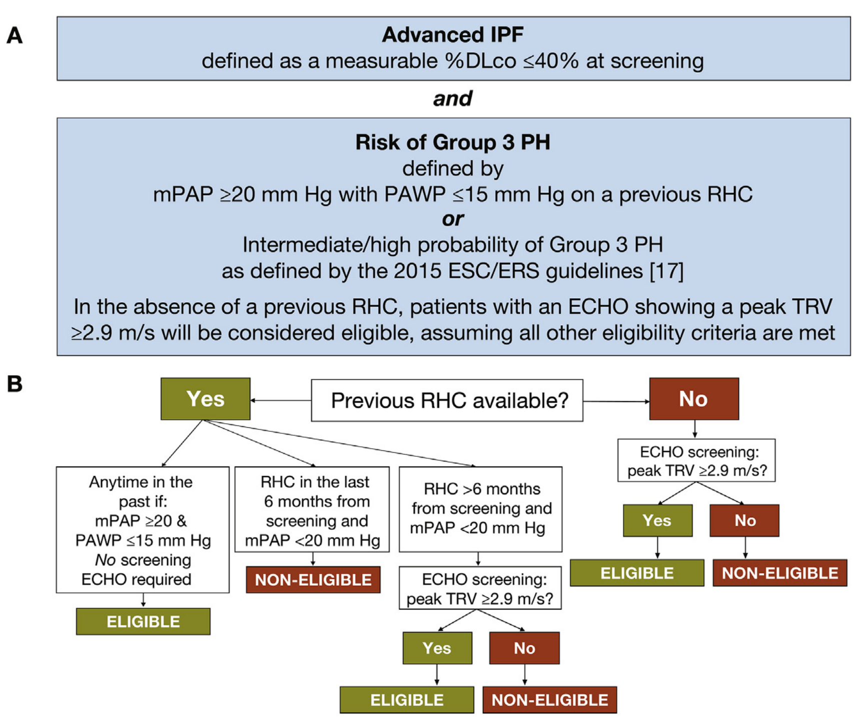

Fig. 2. Key inclusion (A) and eligibility criteria for risk of Group 3 PH (B).
DLco diffusing capacity for carbon monoxide; *ECHO* echocardiogram; *ERS* European Respiratory Society; *ESC* European Society of Cardiology; *IPF* idiopathic pulmonary fibrosis; *mPAP* mean pulmonary arterial pressure; *PAWP* pulmonary artery wedge pressure; *PH* pulmonary hypertension; *RHC* right-heart catheterisation; *TRV* tricuspid valve regurgitation velocity. Adapted from Ref. [17].

Table 4
Secondary efficacy and safety objectives and corresponding endpoints.

Secondary efficacy objective	Secondary efficacy endpoints
To evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone	•Progression-free survival, defined as time to decline in 6MWD of ≥15% compared with baseline, respiratory-related, non-elective hospitalisation or death from any cause •Proportion of patients with decline in 6MWD of ≥15% from baseline •Time to respiratory-related, non-elective hospitalisation •Time to death from any cause •Lung transplant •Time to all-cause, non-elective hospitalisation •Time to respiratory-related death •Change from baseline in transthoracic echocardiography parameters •Change from baseline in pulmonary function tests •Change from baseline SpO_2, at rest and during the 6MWT •WHO functional class •Dyspnoea (assessed by the UCSD-SOBQ) •Health-related quality of life (assessed by the SGRQ) •N-terminal pro-brain natriuretic peptide level
Safety objective	Safety endpoints
To evaluate the safety of adding sildenafil compared with placebo to pirfenidone	•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 ECGs •Study discontinuation or study drug discontinuation

6MWD 6-minute walk distance; *6MWT* 6-minute walk test; *ECG* electrocardiogram; *SGRQ* St George's Respiratory Questionnaire; *SpO_2* oxyhaemoglobin saturation; *UCSD-SOBQ* University of California, San Diego Shortness of Breath Questionnaire; *WHO* World Health Organization.

exposure to sunlight, wear sunscreen with sun protection factor ≥50 and ultraviolet (UV)-A and UV-B protection and to wear clothing that protects against the sun. Dose reduction or temporary treatment discontinuation may be necessary in some patients with photosensitivity reaction or rash. Patients will be advised to take pirfenidone with food to reduce the likelihood of developing gastrointestinal (GI) symptoms, and dose modifications may be necessary in some patients with GI AEs. Due to the known mechanism of action of sildenafil, the effect of vasodilation on a patient's underlying medical condition should also be considered.

If clinically significant treatment-emergent AEs or toxicity are experienced by patients in either treatment group, treatment of symptoms and/or temporary dose reduction, interruption or discontinuation will be considered by the investigator. Following a treatment interruption of more than 14 days, pirfenidone can be retitrated at one capsule three times a day from Days 1 to 7; two capsules three times a day from Days 8 to 14; and three capsules three times a day from Day 15 onwards.

Liver function tests will be performed at screening and Day 1 prior to study drug initiation, and at each subsequent clinic visit during the study. In the event of a significant elevation in liver aminotransferases (> 3–5 × upper limit of normal [ULN]), pirfenidone dose will be adjusted or discontinued.

2.5. Statistical methods

There are no reference data available on the use of pirfenidone in this patient population with a measurable DLco ≤40% predicted and mPAP ≥20 mm Hg on RHC or ECHO of intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TRV ≥2.9 m/s) [17]. Approximately 176 patients are planned to be enrolled at 75 centres in Canada, Europe (EU), Eastern Europe, the Middle East and South Africa.

Patients will be randomised 1:1 to the two treatment groups. 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% in patients with advanced IPF (DLco < 35%) by 52 weeks in the CAPACITY (Study 004 and Study 006) and ASCEND (Study 016) trials [23,24], 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% (relative reduction of 25%) in disease progression rate is considered a clinically meaningful treatment benefit.

Patient demographics and baseline characteristics, such as sex, age and race, will be summarised by treatment arm using means or medians for continuous variables and proportions for categorical variables. Primary and secondary efficacy analyses will include all randomised patients, with patients grouped according to their assigned treatment. Primary analysis of the composite efficacy endpoint will be based upon the intent-to-treat population, with no imputation for patients who discontinue treatment prematurely. A sensitivity analysis will repeat the above analysis in the per-protocol population. Rates of disease progression in each treatment group will be compared by means of a Chi-square test with a one-sided significance level of $\alpha = 0.05$. For secondary efficacy endpoint assessment, progression-free survival will be analysed using Kaplan–Meier techniques, and the treatment arms will be compared by the log-rank test; hazard ratios and 95% confidence intervals will be calculated by Cox proportional hazards models. The proportions of patients with decline in 6MWD of ≥15% from baseline will be compared using a Chi-square test with a one-sided significance level of $\alpha = 0.05$. Change in 6MWD from baseline to 12 months will be compared using a rank ANCOVA model.

Safety will be assessed by AEs, AEs of Grade ≥3, serious AEs, treatment-related AEs, AEs leading to study drug discontinuation or interruption, death, exposure to study medication, premature withdrawal from study and from study medication, laboratory parameters, ECG and vital signs, and summarised by treatment arm. Time to discontinuation will be displayed using Kaplan–Meier techniques.

There are no planned interim analyses for efficacy. Safety interim analyses will be performed regularly by an independent Data Monitoring Committee.

3. Discussion

This study is designed to assess the treatment of patients with advanced disease who have evidence suggestive of PH most likely caused by IPF. PH is a major contributor to morbidity and mortality in patients with advanced IPF [11,15,16]. A higher mPAP at initial evaluation of patients with IPF may be an independent predictor of prognosis [40], and elevated pulmonary vascular resistance (PVR) may be a strong haemodynamic predictor of early mortality in patients with diffuse fibrotic lung disease, including IPF, regardless of the severity of fibrosis [41].

In a retrospective analysis of consecutive patients with advanced IPF (patients undergoing pre-transplant RHC), PH was present in 31.6% (25/79) of cases [15]. In addition, PH was suspected at baseline on transthoracic ECHO in 17.2% of patients with IPF enrolled in the INSIGHTS-IPF registry [42] , while 40% of patients enrolled in the PROOF registry had elevated sPAP as measured by ECHO [43]. PH in the context of pulmonary disease was present in 14% of patients with IPF and mild-to-moderate physiological impairment enrolled in the ARTEMIS-IPF study, as defined by baseline mPAP ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg by RHC [44]. Guidelines suggest a diagnosis of likely PH can be made when sPAP is > 50 mm Hg by ECHO [45].

To date, approved therapies used to treat PH have not been effective at targeting the underlying fibrotic parenchymal changes that occur in IPF [18–21]. Studies of ET receptor antagonists have specifically targeted fibrosis rather than the complicating PH. Although a few studies have shown that targeted therapy with PDE-5 inhibitors or prostacyclin analogues can improve exercise capacity [46], the use of targeted therapy in patients with PH in the context of significant lung disease is not supported by evidence derived from randomised controlled trials, and there is no agent with regulatory approval for this indication.

Similarly, approved antifibrotic therapies for IPF are unlikely to have a notable effect on the vascular abnormalities observed in patients with interstitial lung disease, though no studies have addressed this directly. With the approval of two antifibrotic therapies for IPF, the future of IPF management is likely to involve add-on, combination and sequential therapies, including the use of targeted therapies on a background of an approved drug with established efficacy. Indeed, a shift from monotherapy to combination therapy has proven efficacious in other lung diseases, including lung cancer, chronic pulmonary obstructive disease, asthma and PAH [47]. Therefore, combination treatment constitutes a promising approach to treat patients with advanced IPF and risk of PH.

Sildenafil, a PDE-5 inhibitor that stabilises cGMP, enhances the vasodilatory effects and platelet anti-aggregatory activity of NO and inhibits thrombus formation; these pleiotropic properties may render it attractive as an add-on treatment for IPF [16,32,48]. Additionally, *ex vivo* experiments using pulmonary arteries from healthy donors and patients with IPF or PH associated with IPF revealed a direct relaxant/anti-contractile and anti-remodelling role for sildenafil [48].

In patients with IPF and secondary PH, the expected benefits of pirfenidone and sildenafil combination treatment relate to the anticipated improvements in pulmonary haemodynamics by sildenafil in patients with PH in the context of IPF, while the progression of fibrosis and decline in lung function will be targeted by pirfenidone. It is also possible that the addition of sildenafil to pirfenidone therapy could improve ventilation-perfusion matching, and thus gas exchange, through preferential vasodilatation in well-ventilated areas [48]. A reduction in PVR by sildenafil would be expected to improve mPAP, consequently reducing strain on the right ventricle and improving cardiac output, assuming that left ventricular function and systemic vascular resistance are not adversely affected. Improved ventilation-perfusion matching would be expected to improve gas transfer in the lung and have a beneficial effect on functional exercise capacity, such as 6MWD. These haemodynamic effects of sildenafil, in combination with the known antifibrotic effects of pirfenidone on slowing the rate of lung function decline, might have a benefit on reducing respiratory decompensation, related hospitalisations and, potentially, mortality.

A concern with the use of vasodilatory drugs is the potential for worsening of ventilation-perfusion mismatching and, consequently, hypoxaemia [16]. However, evidence from preclinical studies showed that sildenafil did not modify the ventilation-perfusion ratio in a bleomycin model of pulmonary fibrosis associated with PH [48]. In a recent pilot study, sildenafil did not have a significant effect on gas exchange in patients with severe PH-associated and chronic obstructive pulmonary disease [49]. In patients with PH secondary to IPF, sildenafil improved haemodynamics by maintaining short-term ventilation-perfusion matching [29]. Importantly, in STEP-IPF, no significant differences in the incidence of death, acute exacerbations, AEs or serious AEs were found between patients with IPF receiving sildenafil and those receiving placebo [32].

In May 2016, a study assessing the efficacy and safety of riociguat in patients with symptomatic PH associated with idiopathic interstitial pneumonia (RISE-IIP; NCT02138825) was prematurely terminated following a recommendation by the Data Monitoring Committee. Patients receiving riociguat were observed to be at an increased risk for death and other serious AEs compared with those receiving placebo [22]. Although riociguat targets the NO pathway, it has a different mechanism of action to sildenafil, and acts by enhancing cGMP production, whereas sildenafil works by preventing cGMP degradation. Preclinical studies of sildenafil have revealed no deleterious effect on hypoxia [48]. Both pirfenidone and sildenafil have well-characterized safety profiles and are associated with AEs of mild-to-moderate severity without significant clinical consequence [50,51]. A small case-control study suggested that pirfenidone and sildenafil may be used safely in combination in patients with advanced IPF [35]. To address concerns raised following the early termination of RISE-IIP, and to minimize any potential risk, a safety plan has been established for the present study, including appropriate eligibility criteria, dose modification and/or discontinuation guidelines for identified risks and regular monitoring by the independent Data Monitoring Committee.

The pharmacokinetics of pirfenidone and sildenafil in isolation have been well characterised. Pirfenidone is primarily metabolised in the liver by CYP1A2, with some contribution from other CYPs, and approximately 80% of pirfenidone or its metabolites are eliminated by the kidney following oral administration [52]. Sildenafil is rapidly absorbed, with peak plasma concentrations reached within 1 hour of oral administration, and is cleared primarily by metabolism (CYP3A4 [major route]; CYP2C9 [minor route]), with no parent drug detectable in urine or faeces. While no drug–drug interactions have been reported, an interaction between sildenafil and pirfenidone cannot be eliminated [53,54].

There are a number of distinctive aspects of the present study as compared with previous studies, including eligibility based on DL_{CO}, RHC and ECHO, the use of a composite primary outcome measure and the strengthened assessment of 6MWD using parameters collected during the 6MWT (Table 5).

While the presence of PH (defined as an mPAP of ≥ 25 mm Hg at rest on RHC) is associated with an increased risk of mortality for patients with IPF [12], data suggest that an mPAP of 17 mm Hg may be the best discriminator of mortality [37]. Therefore, an mPAP ≥ 20 mm Hg has been selected as an inclusion criterion based on RHC. The 2015 ESC/ERS guidelines on the management of PH define intermediate/high probability PH based on an ECHO TRV of ≥ 2.9 m/s [17]. Therefore, in the absence of a previous RHC, patients with an ECHO showing a peak TRV ≥ 2.9 m/s will be considered eligible for this study as long as all other criteria are met.

A DL_{CO} of 40% predicted has been selected as an inclusion criteria in order to provide overlap with previous clinical studies of pirfenidone, and, importantly, to increase the likelihood of the study including patients with pulmonary vasculopathy and a risk of PH. Using a DL_{CO} inclusion criterion to define patients with advanced IPF, combined with a RHC/ECHO inclusion criterion, increases the probability that PH will be present in the study population (Table 5).

The composite primary endpoint will consider exercise capacity (using the 6MWT) as well as respiratory-related non-elective hospitalisations and all-cause mortality. This has been expanded from the primary endpoint of 6MWD used in previous studies of sildenafil. The composite endpoint has increased robustness, since it considers respiratory-related hospitalisations as well as hard outcomes, such as all-cause mortality, which is considered the most robust endpoint in therapeutic clinical trials. In the pivotal studies of pirfenidone (CAPACITY and ASCEND), progression-free survival was defined as time to death or disease progression (confirmed $\geq 10\%$ absolute decline in percent predicted FVC or confirmed ≥ 50-m decline in 6MWD) [7]. However, the use of a 50-m decline in 6MWD as an endpoint is not appropriate in patients with advanced disease, such as those who will be enrolled in the present study, owing to the low baseline observed in these patients [55].

Finally, by strengthening the definition of the primary endpoint 6MWT assessment using additional parameters collected during the test, patients experiencing a decline will not need to perform an additional 6MWT to reconfirm the decline, thereby reducing the need for a further clinic visit.

Table 5
Comparison of MA29957 with Phase III trials of pirfenidone and sildenafil in IPF.

	CAPACITY	ASCEND	STEP-IPF	MA29957
Inclusion criteria				
FVC, % predicted	≥50%*	≤90% and ≥50%	–	–
DLco, % predicted	≥35%*	≤90% and ≥30%	< 35%	≤40
RHC criteria	–	–	–	mPAP ≥20 mm Hg with PAWP ≤15 mm Hg on a previous RHC
ECHO criteria	–	–	–	Peak TRV ≥2.9 m/s†
6MWD	150 m*	≥150 m	–	100–450 m
Exclusion criteria				
6MWD	–	–	< 50 m; difference of > 15% in 6MWD between two pre-randomisation walks	–
Key features				
Primary endpoint	Change in % predicted FVC from baseline to Week 72	Change from % predicted FVC at baseline to Week 52	Presence or absence of improvement of ≥20% in 6MWD at Week 12 vs. baseline	Proportion of patients with disease progression over 52 weeks‡
Study duration	72 weeks	52 weeks	12 weeks	52 weeks

*Either a % predicted FVC or % predicted DLco ≤90%.
†In the absence of a previous RHC assuming all other eligibility criteria are met.
‡Defined by a composite endpoint of relative decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalisations or all-cause mortality.
6MWD 6-min walk distance; *6MWT* 6-min walk test; *DLco* diffusing capacity for carbon monoxide; *ECHO* echocardiogram; *FVC* forced vital capacity; *IPF* idiopathic pulmonary fibrosis; *mPAP* mean pulmonary arterial pressure; *PAWP* pulmonary artery wedge pressure; *RHC* right-heart catheterisation; *TRV* tricuspid valve regurgitation velocity [23,24,32].

4. Conclusions

In conclusion, this study will investigate the use of sildenafil added to pirfenidone in patients with advanced IPF and secondary PH, for whom no effective therapies are currently available. Combination treatment may address an unmet need in these patients by providing effective therapies that target PH in addition to the underlying fibrotic process.

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List of abbreviations

6MWD 6-minute walk distance
6MWT 6-minute walk test
AE Adverse event
cGMP Cyclic guanine monophosphate
CYP Cytochrome
DLco Diffusing capacity for carbon monoxide
ECG Electrocardiogram
ECHO Echocardiogram
ERS European Respiratory Society
ESC European Society of Cardiology
FEV_1 Forced expiratory volume in 1 s
FVC Forced vital capacity
GI Gastrointestinal
IPF Idiopathic pulmonary fibrosis
mPAP Mean pulmonary arterial pressure
NO Nitric oxide
PAH Pulmonary arterial hypertension
PDE-5 Phosphodiesterase-5
PH Pulmonary hypertension
PVR Pulmonary vascular resistance
QoL: Quality of life
RHC Right-heart catheterisation
SaO_2 Oxyhaemoglobin saturation
sPAP Systolic pulmonary arterial pressure
TRV Tricuspid valve regurgitation velocity
ULN Upper limit of normal
UV Ultraviolet

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