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Doctopic: Primary Research

Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial

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Summary

Background The benefit of sildenafil in patients with advanced idiopathic pulmonary fibrosis (IPF) at risk of poor outcomes from pulmonary hypertension, whether already present or likely to develop, is uncertain. We aimed to assess the efficacy and safety of sildenafil added to pirfenidone versus placebo added to pirfenidone for 52 weeks in patients with advanced IPF and at risk of group 3 pulmonary hypertension.

Methods We did a multicentre, international, double-blind, randomised, placebo-controlled, phase 2b study at 56 university clinics, research hospitals, and tertiary sites in Canada, Europe (in Belgium, Czech Republic, Germany, Greece, Hungary, Italy, the Netherlands, Spain, and Turkey), Israel, and Africa (in Egypt and South Africa). Eligible patients (aged 40–80 years) had advanced IPF (carbon monoxide diffusing capacity ≤40% predicted at screening), and were at risk of group 3 pulmonary hypertension (mean pulmonary artery pressure of ≥20 mm Hg with pulmonary artery wedge pressure of ≤15 mm Hg on previous right-heart catheterisation, or intermediate or high probability of group 3 pulmonary hypertension on echocardiography as defined by the 2015 European Society of Cardiology and European Respiratory Society guidelines). Patients were randomly assigned 1:1 to oral sildenafil tablets (20 mg three times daily) or placebo, both in addition to oral pirfenidone capsules (801 mg three times daily), using a validated interactive voice-based or web-based response system with permuted block randomisation, stratified by previous right-heart catheterisation (yes or no) and forced expiratory volume in 1 s to forced vital capacity ratio (<0·8 or ≥0·8). The composite primary endpoint was disease progression, defined as either a decline in 6-min walk distance (defined as >25% decline from baseline associated with worsening oxygen saturation, Borg score, or increased oxygen requirements), respiratory-related admission to hospital, or all-cause mortality, after 52 weeks and was assessed in the intention-to-treat population; safety was assessed in all patients who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov, NCT02951429, and is no longer recruiting. The 11-month safety follow-up is ongoing.

Findings Between Jan 13, 2017, and Aug 30, 2018, 247 patients were screened for eligibility, 177 of whom were randomly assigned to a treatment group (n=88 sildenafil; n=89 placebo) and were assessed for the primary outcome. There was no difference in the proportion of patients with disease progression over 52 weeks between the sildenafil (64 [73%] of 88 patients) and placebo groups (62 [70%] of 89 patients; between-group difference 3·06% [95% CI −11·30 to 17·97]; p=0·65). Serious treatment-emergent adverse events were reported in 54 (61%) patients in the sildenafil group and 55 (62%) patients in the placebo group. Treatment-emergent adverse events leading to mortality occurred in 22 (25%) patients in the sildenafil group and 26 (29%) in the placebo group.

Interpretation Addition of sildenafil to pirfenidone did not provide a treatment benefit versus pirfenidone plus placebo up to 52 weeks in patients with advanced IPF and risk of pulmonary hypertension. No new safety signals were identified with either treatment. Although the absence of a beneficial treatment effect suggests that sildenafil is not an appropriate treatment in the overall population, further research is required to establish if specific subgroups of patients with IPF might benefit from sildenafil.

Funding F Hoffmann-La Roche.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease associated with a poor 5-year survival rate; if treatment is not initiated, the survival rate is lower than that reported for many cancers.[1,2] Two antifibrotic drugs have been shown to slow the progression of IPF;[3–5] however, the pivotal trials for these drugs did not include patients with advanced IPF and thus it is not

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Research in context

Evidence before this study

Previous trials of group 1 pulmonary arterial hypertension treatments in patients with interstitial lung disease have been disappointing. However, because pulmonary vascular impairment exists in idiopathic pulmonary fibrosis (IPF) before pulmonary hypertension becomes apparent, it is possible that earlier use of targeted pulmonary hypertension therapy in those patients at risk of poor outcomes from pulmonary hypertension, whether already present or likely to develop during the trial period, might be a more promising approach. Furthermore, although there are two antifibrotic drugs that have been shown to slow disease progression in patients with IPF, the pivotal trials did not include patients with advanced IPF and it is therefore not known whether antifibrotic drugs are equally effective in this population. We searched PubMed from database inception to May 20, 2020, for reports published in any language using the search terms (["sildenafil"] AND ["IPF" OR "idiopathic pulmonary fibrosis"]), which yielded 42 articles. After excluding publications that were not written in English, 38 articles remained. To focus on randomised controlled trials, all other publications were excluded, which left seven articles. Of these remaining articles, five described sildenafil monotherapy in patients with IPF. The other two articles reported data from the INSTAGE trial and involved sildenafil in combination with nintedanib in patients with advanced IPF and did not show conclusive benefits for the combination. Thus, our search did not identify any randomised controlled trials investigating sildenafil in combination with pirfenidone in patients with advanced IPF.

Added value of this study

To the best of our knowledge, our study is the first randomised controlled trial to evaluate the efficacy and safety of sildenafil in combination with pirfenidone up to 52 weeks in patients with advanced IPF at risk of group 3 pulmonary hypertension, a population in which there are no prospectively acquired data of pirfenidone treatment. Although there was no significant difference for sildenafil plus pirfenidone versus placebo plus pirfenidone in the proportion of patients with disease progression up to 52 weeks or between treatment groups for any of the secondary endpoints, no new safety signals were observed with either treatment. The evidence from this study suggests a tolerability of pirfenidone in patients with advanced IPF that is similar to that shown in the pivotal phase 3 ASCEND and CAPACITY trials, and the open-label extension study, RECAP.

Implications of all the available evidence

There are no approved therapies for group 3 pulmonary hypertension and there is little evidence of antifibrotic drugs use in patients with advanced IPF; therefore, the results of this study are important for patients with advanced IPF at risk of group 3 pulmonary hypertension and the clinicians involved in their treatment. The results of this study suggest that sildenafil should not be used in this group of patients; however, further research is required to establish if specific subgroups of patients might benefit from treatment with sildenafil. Furthermore, to the best of our knowledge, this study provides the first prospective data of pirfenidone in patients with advanced IPF.

known whether antifibrotic drugs are equally effective in this population.

Moreover, in advanced IPF, comorbidities have a substantial effect on morbidity and mortality, particularly so with pulmonary vascular disease because patients with this disease have a high risk of developing pulmonary hypertension in the year after diagnosis.[6] Pulmonary hypertension affects approximately 30–50% of patients with clinically significant pulmonary disease (group 3 pulmonary hypertension) and is associated with a three-fold increase in mortality compared with people with pulmonary disease and no pulmonary hypertension.[7] There are no approved therapies for group 3 pulmonary hypertension,[7] and trials of treatments for group 1 pulmonary arterial hypertension in patients with interstitial lung disease have been disappointing.[8–10] However, because pulmonary vascular impairment exists in patients with IPF before pulmonary hypertension becomes apparent, we hypothesised that sildenafil might have a beneficial role in treating patients with advanced IPF who are at risk of poor outcomes from pulmonary hypertension, whether already present or likely to develop during the trial period.

Sildenafil, a phosphodiesterase-5 inhibitor approved for group 1 pulmonary arterial hypertension,[7,11] causes pulmonary vasodilation, resulting in improved haemodynamics in patients with this disease.[7,12] Trials of sildenafil monotherapy in IPF have been inconclusive, possibly because of short observation periods, small sample sizes, or primary endpoint selection.[13–17] Consequently, the international treatment guidelines for IPF give a conditional recommendation against sildenafil, citing an absence of evidence to indicate any benefit to outcomes, including mortality, acute exacerbations, or dyspnoea.[18] However, use of sildenafil earlier in the course of pulmonary vascular disease in IPF has not been robustly evaluated.

We aimed to evaluate the efficacy, safety, and tolerability of sildenafil plus pirfenidone versus placebo plus pirfenidone for 52 weeks in patients with advanced IPF with, or at risk for developing, group 3 pulmonary hypertension.

Methods

Study design and participants

This multicentre, international, double-blind, randomised, placebo-controlled, phase 2b study was done at 56 university clinics, research hospitals, and tertiary sites in Canada, Europe (in Belgium, Czech Republic, Germany, Greece, Hungary, Italy, the Netherlands, Spain, and Turkey), Israel, and Africa (in Egypt and South Africa). Study methods have been previously described.[19] Eligible patients were aged 40–80 years and had advanced IPF, defined as measurable diffusing capacity for carbon monoxide (DLco) of 40% or less predicted at screening; and either at risk of group 3 pulmonary hypertension (defined as a mean pulmonary arterial pressure of ≥20 mm Hg with pulmonary artery wedge pressure of ≤15 mm Hg on previous right-heart catheterisation) or with intermediate or high probability of having group 3 pulmonary hypertension on echocardiography as defined by the 2015 European Society of Cardiology and European Respiratory Society guidelines.[7] Patients were excluded if they had a history of pulmonary hypertension other than group 3 pulmonary hypertension due to interstitial lung disease; history of clinically significant cardiac or pulmonary disease (other than IPF or group 3 pulmonary hypertension); history of drug or toxin use known to cause pulmonary arterial hypertension; forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio of less than 0·70 after bronchodilation; tobacco use in the previous 3 months; peripheral capillary oxygen saturation (SpO_2) at rest of less than 92% with 6 L or more of supplemental oxygen; extent of emphysema greater than extent of fibrotic changes on any previous high-resolution CT scan; or if they met any exclusion criteria based on pirfenidone or sildenafil reference safety information.[19]

At screening, patients were required to have had an IPF diagnosis for at least 3 months and to have received pirfenidone for at least 12 weeks at 1602–2403 mg per day. No new or ongoing grade 2 or worse pirfenidone-related adverse events or treatment interruptions of longer than 7 days were permitted during the 4 weeks before screening. A 6-min walk distance of 100–450 m was also required.

The study was done in accordance with the ethical principles of the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations for the countries in which the study was done. Written informed consent was obtained from each participant by the study investigator before any procedures were done. The study protocol, informed consent forms, information given to the patient, and relevant supporting information were submitted to the independent review board or ethics committee by the principal investigator, and were reviewed and approved by the independent review board or ethics committee before the study started.

Randomisation and masking

Participants were randomly assigned 1:1 to pirfenidone plus sildenafil or pirfenidone plus placebo. Randomisation was done using a validated interactive voice-based or web-based response system hosted by S-Clinica (Brussels, Belgium) using permuted block randomisation (statistically generated blocks). Randomisation was stratified by previous right-heart catheterisation (yes or no) and FEV_1 to FVC ratio (<0·8 or ≥0·8) to ensure an equal distribution of patients with some degree of pulmonary obstruction in both treatment groups.

Investigational site personnel and patients were masked to treatment assignment. To maintain masking, the sildenafil and placebo treatments were identical in appearance. Unmasking was permitted in emergency situations for patient management, such as the incidence of a serious adverse event, in which the study investigator would be able to break the treatment code by contacting S-Clinica. Maintenance of masking was continually assessed by the study coordinator at each investigational site. The database was locked until statistical analysis.

Procedures

Patients were instructed to take oral pirfenidone capsules at the approved dose for IPF of 801 mg three times daily, at the same times each day, with food, to achieve a dose within the accepted range of 1602–2403 mg per day (dose modifications were permitted), and oral sildenafil tablets at the approved dose for pulmonary arterial hypertension of 20 mg three times daily, or matched placebo three times daily (figure 1). Patients kept a diary to record daily dosing adherence.

There was a run-in period of 12 weeks in countries where patients were not otherwise able to receive

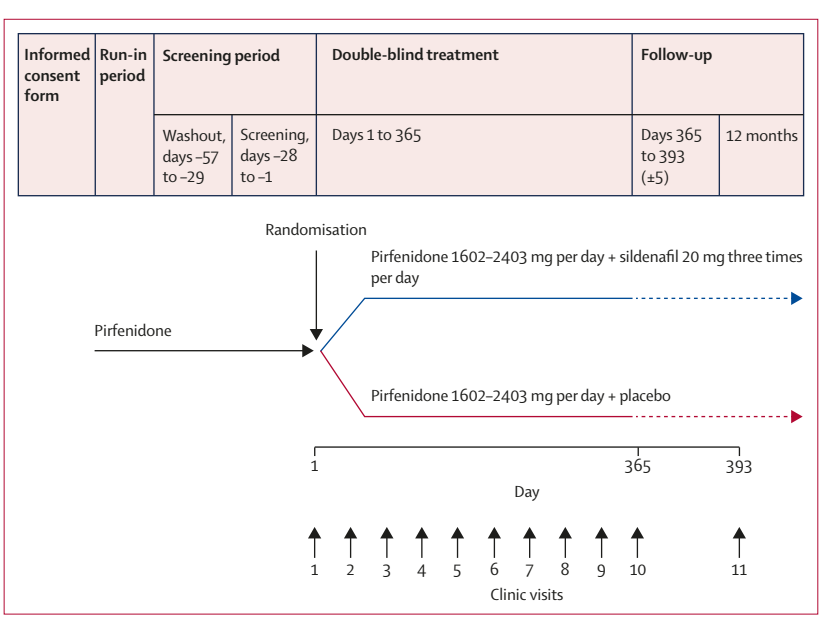

Figure 1: **Study design**
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pirfenidone because of reimbursement issues. Patients receiving a prohibited medication had a 28-day washout period, which could be included in the run-in if applicable. Patients not taking a prohibited medication could directly enter screening. The screening period was up to 28 days, during which, eligibility based on the inclusion and exclusion criteria was evaluated. As soon as eligibility was confirmed, patients returned for the baseline visit (day 1) of the 52-week, double-blind treatment period including 10 clinic visits. Patients then stopped receiving sildenafil or placebo but continued to receive pirfenidone during a safety follow-up of 4 weeks (with one clinic visit at the end of this 4-week period, with a 5-day leeway). During the 11-month safety follow-up, patients were offered continued access to pirfenidone with evaluation of safety approximately every 3 months. A schedule of assessments done at each visit is shown in the appendix (pp 3–7).

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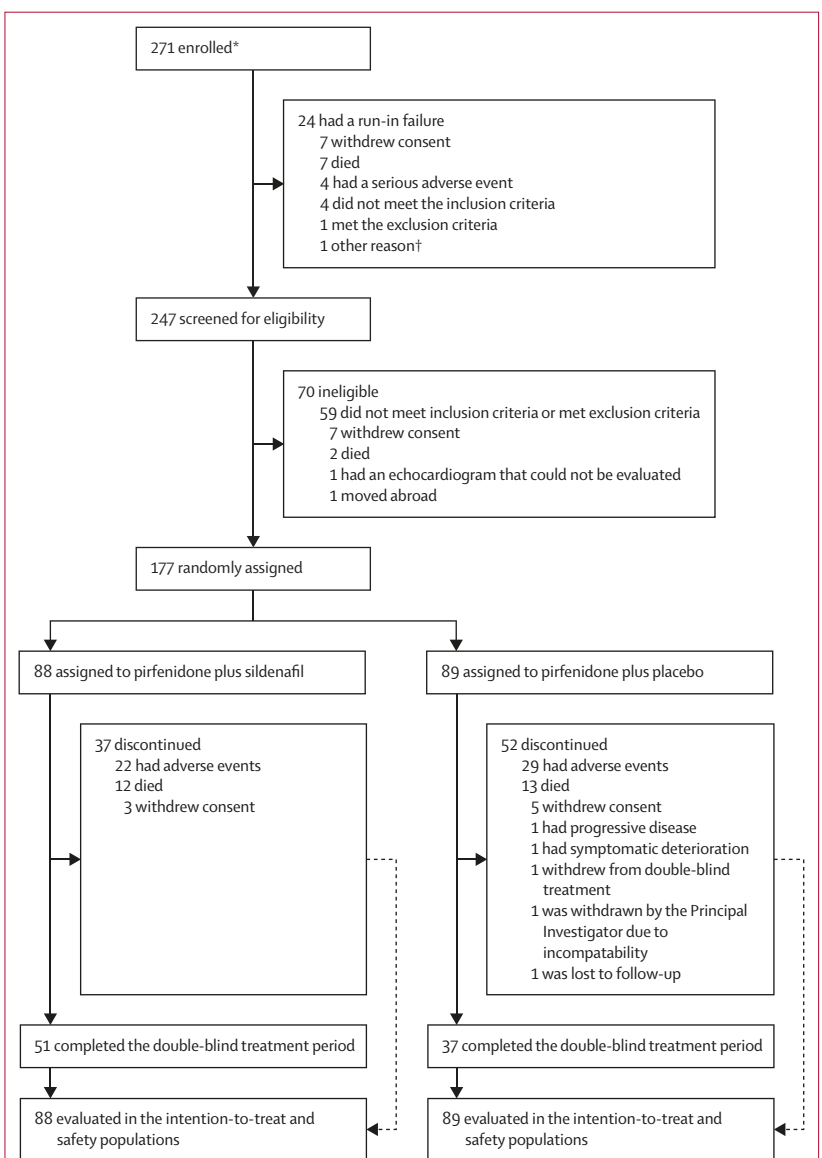

Figure 2: **Trial profile**
*Enrolled patients signed informed consent form before run-in or screening. †No information on run-in failure available.

Outcomes

The primary endpoint was the proportion of patients with disease progression over 52 weeks, defined using a composite endpoint: relevant decline in 6-min walk distance from baseline, respiratory-related non-elective admission to hospital, or all-cause mortality. Relevant decline from baseline in 6-min walk distance was specified as more than 25% decline, or 15–25% decline if accompanied by at least one of the following during the 6-min walk test: worsening SpO_2 desaturation; worsening of the maximum Borg scale rating; or increased oxygen requirements (defined as an increase versus the flow of oxygen required at baseline). The composite primary endpoint was expanded from the primary endpoint of 6-min walk test used previously in this patient population and in clinical trials of pulmonary arterial hypertension.[14–16,20] The primary outcome was assessed at each participating centre.

Secondary endpoints included analyses of the individual components of the composite primary endpoint, progression-free survival, all-cause non-elective hospitalisation, and respiratory-related mortality, all including time-to-event analyses and all up to 52 weeks. Also assessed as secondary endpoints were changes from baseline to 52 weeks in transthoracic echocardiography parameters, pulmonary function tests (FVC, FEV_1, FEV_1 to FVC ratio, and DLco), 6-min walk test parameters, the University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ), the St George's Respiratory Questionnaire (SGRQ), and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration. WHO functional class, the proportion of patients receiving a lung transplant, and the incidence of acute exacerbations (adjudicated by investigators) were also evaluated up to week 52 as secondary endpoints.

Safety outcomes included treatment-emergent adverse events (including serious treatment-emergent adverse events [defined as those that meet any of the following criteria: is fatal, is life-threatening, requires or prolongs hospitalisation, results in persistent or clinically significant disability, or is a congenital anomaly in an infant born to a mother exposed to study drug] and severe treatment-emergent adverse events [refers to the intensity of an event]), and mortality. Treatment-emergent adverse events and causes of mortality were coded using the Medical Dictionary for Regulatory Activities Version 22.1.

Statistical analysis

There are no reference data available on pirfenidone in patients with predicted DLco of 40% or less and risk of

group 3 pulmonary hypertension.[7] The planned sample size of approximately 176 patients was based on the primary endpoint, assuming 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 week 52 in the pivotal pirfenidone trials CAPACITY[3] and ASCEND,[4] and assuming an additive effect of sildenafil on pirfenidone, a disease progression rate of 54% in the combination treatment group was assumed, and an absolute difference of 18% (relative reduction of 25%) was considered a clinically meaningful treatment benefit.

Primary and secondary endpoints were assessed in the intention-to-treat population, which included all randomly assigned patients. During the primary analysis, disease progression rates in each treatment group were compared using a χ^2 test with a one-sided significance level of α=0·05. The individual components of the primary endpoint (progression-free survival, all-cause hospitalisation, and respiratory-related mortality), were analysed using Kaplan-Meier techniques and the treatment groups were compared using the log-rank test. Hazard ratios (HR) and 95% CIs were calculated by Cox proportional hazards models. The statistical analyses of the other endpoints are described in the appendix (p 2).

Safety was assessed in the safety analysis set, which included all randomly assigned patients who received at least one dose of the study drug. Safety was summarised descriptively for each treatment group. All statistical analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02951429.

Role of the funding source

The funder[A: we don't need to repeat who the funder is] and its designees, designed the study and analysed the data, and were involved in data interpretation and writing of the manuscript, in collaboration with the academic authors. The funder was not involved in the collection of data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2017, and Aug 30, 2018, 247 patients were screened for eligibility, 177 of whom were randomly assigned to either the pirfenidone plus sildenafil group (n=88; the sildenafil group) or the pirfenidone plus placebo group (n=89; the placebo group; figure 2). 37 (42%) of 88 patients in the sildenafil group and 52 (58%) of 89 patients in the placebo group discontinued early from double-blind treatment. Reasons for early discontinuation are shown in the appendix (p 8) and time to double-blind treatment discontinuation is shown in appendix (p 14).

The majority of baseline characteristics did not differ substantially between treatment groups (table 1);

	Pirfenidone plus sildenafil (n=88)	Pirfenidone plus placebo (n=89)
Age at screening, years	70·0 (63·5–74·0)	69·0 (65·0–74·0)
Men	69 (78%)	65 (73%)
Women	19 (22%)	24 (27%)
Race		
White	85 (97%)	88 (99%)
Asian	1 (1%)	0
Black or African American	0	1 (1%)
Native Hawaiian or other Pacific Islander	1 (1%)	0
Unknown	1 (1%)	0
Body-mass index, kg/m²	27·1 (24·5–30·1)	27·2 (23·6–29·6)
NT-proBNP, pg/mL	125·5 (57·5–274·5)*	161·0 (78·0–402·0)†
History of emphysema	12 (14%)	9 (10%)
Smoking status		
Never	31 (35%)	27 (30%)
Current	0	0
Former	57 (65%)	62 (70%)
Pack-years for former smokers, years	20·0 (10·0–45·0)	30·0 (20·0–40·0)
WHO functional class‡		
Class I	0	0
Class II	39 (44%)	25 (28%)
Class III	49 (56%)	64 (72%)
Class IV	0	0
Previous right-heart catheterisation available	16 (18%)	17 (19%)
PAP, mm Hg	27·3 (6·8)	28·7 (5·4)
PAWP, mm Hg	11·2 (3·02)	10·2 (3·40)
Echocardiogram done at baseline	81 (92%)	83 (93%)
Systolic PAP, mm Hg	55·9 (20·0)§	58·3 (18·3)¶
Peak TRV, m/s	3·43 (0·60)§	3·57 (0·57)¶
Percent predicted FVC	62·0% (49·5–78·7)	60·0% (49·4–72·0)
FVC, L	2·22 (1·66–2·65)	1·87 (1·39–2·52)
Percent predicted FEV_1	70·2% (57·4–84·4)	67·0% (55·5–83·0)
Percent predicted DLco	26·2% (19·5–33·7)	25·0% (20·0–32·6)
FEV_1:FVC	0·86 (0·81–0·90)	0·87 (0·81–0·91)
6-min walk distance, m	317·5 (230·0–393·0)	260·0 (195·0–351·0)
Required oxygen during the 6-min walk test	43 (49%)	59 (66%)
Stopped the test before 6 min	9 (10%)	14 (16%)
Duration of previous pirfenidone treatment, weeks‖	33·9 (12·9–94·8)	53·6 (14·1–136·6)

Data are median (IQR [Q1–Q3]), n (%), or mean (SD). Where data are presented as median (IQR), the Wilcoxon-rank sum-test was used for the comparison between treatment groups. Where data are presented as mean (SD), the Student's *t* test was used. Categorical variables were compared by χ^2 test. DLco=diffusing capacity for carbon monoxide. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. NT-proBNP=N-terminal pro-brain natriuretic peptide. PAP=pulmonary artery pressure. PAWP=pulmonary artery wedge pressure. TRV=tricuspid regurgitation velocity. *n=84. †n=78. ‡Class I: no limitation of usual physical activity, ordinary physical activity does not cause increased dyspnoea, fatigue, or presyncope. Class II: mild limitation of physical activity, no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope. Class III: marked limitation of physical activity, no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain, or presyncope. Class IV: unable to perform any physical activity at rest and there might be signs of right ventricular failure; dyspnoea, fatigue, or both might be present at rest, and symptoms are increased by almost any physical activity. §n=77. ¶n=83. ‖Previous pirfenidone treatment during run-in period and commercial pirfenidone. Treatment duration of pirfenidone during run-in period is calculated as the weeks between the first and the last intake or screening visit date, whichever occurred first. Treatment duration of previous commercial pirfenidone is calculated as the weeks between the first medication intake to the last medication intake or informed consent date, whichever occurred first. [A: we don't need to provide units for the FEV_1:FVC ratio]

Table 1: **Baseline characteristics of study participants in the intention-to-treat population**

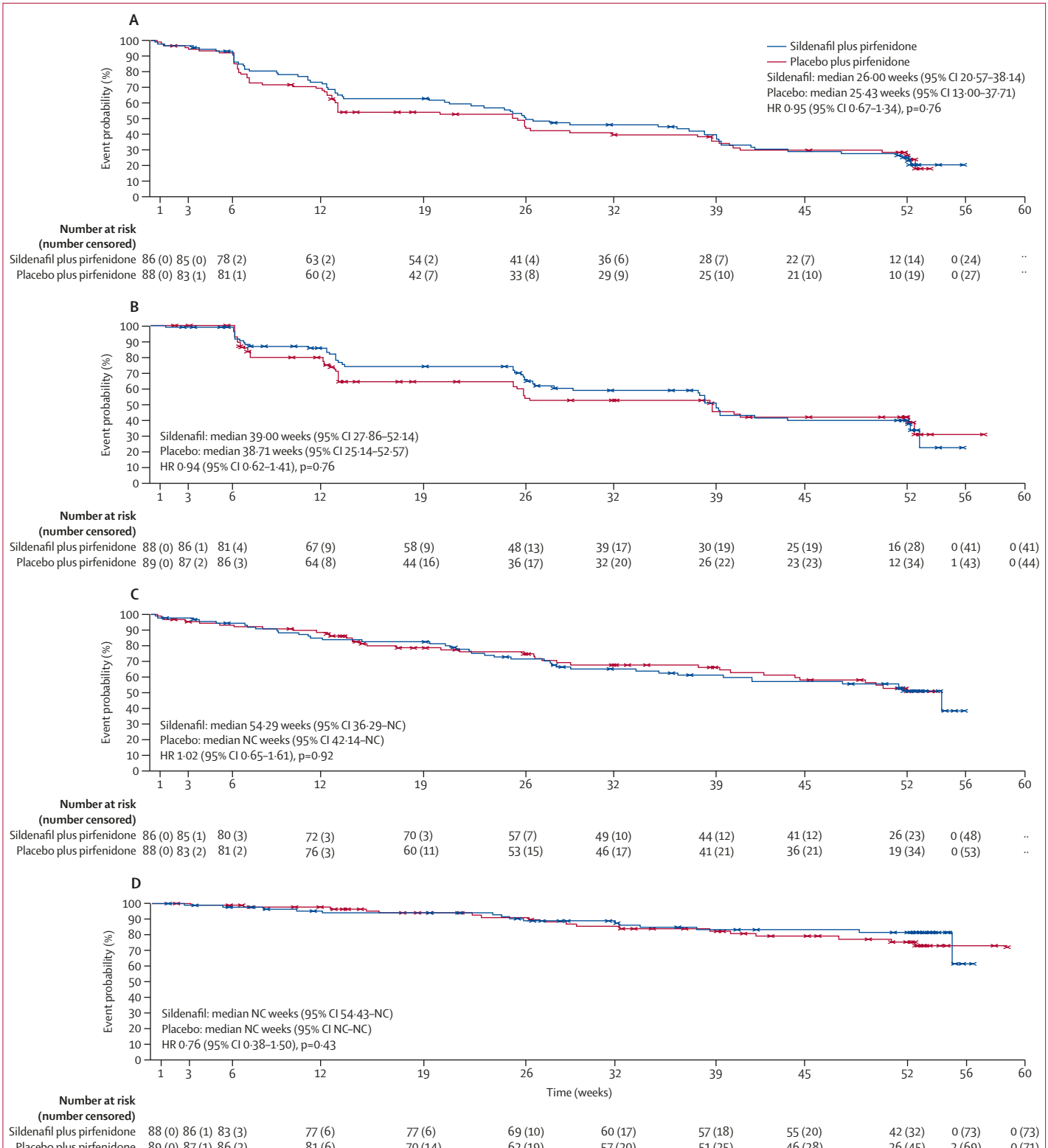

Figure 3: **Time-to-event analyses of composite primary endpoint components in the intention-to-treat population**

(A) Progression-free survival as time to first occurrence of disease progression. (B) Time to first occurrence of relevant decline of 15% or more in 6-min walk distance from baseline. (C) Time to first occurrence of a respiratory-related, non-elective hospitalisation. (D) Time to all-cause mortality. NC=not calculable.

	Pirfenidone plus sildenafil (n=88)	Pirfenidone plus placebo (n=89)	Between-group difference	p value
FVC, mL (95% CI)	−145·0 (−231·3 to −58·6)*	−93·0 (−184·7 to −1·4)†	−51·9 (−159·5 to 55·6)	0·34
NT-proBNP, pg/mL (95% CI)	568·8 (81·6 to 1056·0)‡	775·4 (254·2 to 1296·6)§	−206·6 (−920·0 to 506·9)	0·56
6-min walk distance, m (95% CI)	−80·1 (−107·1 to −53·1)¶	−68·6 (−97·6 to −39·7)‖	−11·5 (−49·5 to 26·5)	0·55

FVC=forced vital capacity. NT-proBNP=N-terminal pro-brain natriuretic peptide. *n=77. †n=76. ‡n=71. §n=69. ¶n=81: 47 patients had a decline from baseline of 15% or more. ‖n=81: 45 patients had a decline from baseline of 15% or more. There were fewer patients in these analyses because of missing values.

Table 2: **Linear slope analyses of estimated changes from baseline in FVC, NT-proBNP, and 6-min walk distance at week 52 in the intention-to-treat population**

however, median 6-min walk distance was greater in the sildenafil group than in the placebo group (p=0·022), and fewer patients in the sildenafil group required oxygen during the 6-min walk test than in the placebo group (p=0·019). Furthermore, a smaller proportion of patients in the sildenafil group were classified as WHO functional Class III than in the placebo group, and a greater proportion of patients in the sildenafil group were classified as WHO functional Class II than in the placebo group (p=0·025).

Other key differences between the groups at baseline were the mean time since IPF diagnosis, which was shorter in the sildenafil group (2·8 years [SD 2·3]) than in the placebo group (3·3 years [2·9]), and the median duration of previous pirfenidone treatment, which was 33·9 weeks (IQR [Q1–Q3] 12·9–94·8) in the sildenafil group and 53·6 weeks (14·1–136·6) in the placebo group. During the study, the median overall treatment durations for sildenafil or placebo, including dose interruptions, were longer in the sildenafil group (52·0 weeks [IQR 28·1–52·4]) than in the placebo group (45·3 weeks [21·9–52·0]).

The primary endpoint and safety outcomes were analysed using data collected during the 52-week double-blind treatment period. As of November, 2019, the 11-month safety follow-up was ongoing, with 91 patients enrolled. The proportion of patients with disease progression up to 52 weeks in the sildenafil group was 64 (73%) of 88 patients, and in the placebo group was 62 (70%) of 89 patients; the between-group difference was 3·06% (95% CI −11·30 to 17·97; p=0·65).

There was no difference in progression-free survival between the two groups (figure 3A). Time-to-event analyses for the composite primary endpoint components are shown in figure 3B–D. Overall, 47 (53%) of 88 patients in the sildenafil group had a decline in 6-min walk distance of at least 15% versus 45 (51%) of 89 patients in the placebo group (HR 0·94 [95% CI 0·62–1·41]). Respiratory-related hospitalisation occurred in 40 (45%) patients in the sildenafil group (51 events) and in 36 (40%) patients in the placebo group (56 events; HR 1·02 [95% CI 0·65–1·61]). All-cause mortality occurred in 15 (17%) patients in the sildenafil group and 18 (20%) patients in the placebo group (HR 0·76 [95% CI 0·38–1·50]; appendix p 9).

All-cause hospitalisation occurred in 46 (52% [73 events]) of 88 patients in the sildenafil group and 41 (46% [65 events]) of 89 patients in the placebo group (HR 1·06 [95% CI 0·70–1·62]). The median time to first occurrence of all-cause hospitalisation was 47·6 weeks (95% CI 28·0–not calculable) in the sildenafil group and 49·9 weeks (32·0–not calculable) in the placebo group (p=0·77). Respiratory-related mortality occurred in 11 (13%) of 88 patients in the sildenafil group and 15 (17%) of 89 patients in the placebo group (HR 0·67 [95% CI 0·31–1·47]).

Descriptive results for NT-proBNP, WHO functional class, 6-min walk test parameters, pulmonary function tests, and transthoracic echocardiography parameters are shown in the appendix (pp 10, 11). Mean 6-min walk distance over time is also shown in the appendix (p 15). Linear slope analyses of changes from baseline in FVC, 6-min walk distance, and NT-proBNP at week 52 are shown in table 2. Ten (11%) of 88 patients in the sildenafil group and four (4%) of 89 patients in the placebo group had one or more acute exacerbation. In the sildenafil group, nine (10%) patients received a lung transplant versus six (7%) patients in the placebo group (these patients subsequently discontinued from the study early as per the protocol requirements). Descriptive results for the SGRQ and UCSD-SOBQ are shown in the appendix (p 12). Rank analysis of covariance analyses that compared treatment groups for the total scores for SGRQ showed median change from baseline to week 52 was 6·77 (IQR −0·02 to 12·87) in the sildenafil group and 11·16 (1·28 to 21·35) in the placebo group (p=0·53). For UCSD-SOBQ, this analysis showed median change from baseline to week 52 was 13·5 (1·0 to 22·0) in the sildenafil group and 22·0 (7·0 to 33·0) in the placebo group (p=0·43).

Treatment-emergent adverse events were reported in 87 (99%) of 88 patients in the sildenafil group and 83 (93%) of 89 patients in the placebo group (table 3). The incidence of treatment-emergent adverse events was generally well balanced between the treatment groups, with the exception of gastrointestinal disorders, which were more prevalent in the sildenafil group versus the placebo group (30 [34%] of 88 patients *vs* 14 [16%] of 89 patients). 31 (35%) patients in the sildenafil group and 30 (34%) patients in the placebo group were judged

	Pirfenidone plus sildenafil (n=88)	Pirfenidone plus placebo (n=89)
Any treatment-emergent adverse event	87 (99%)	83 (93%)
Treatment-related	31 (35%)	30 (34%)
Serious	54 (61%)	55 (62%)
Treatment-related and serious	2 (2%)	4 (5%)
Severe	65 (74%)	66 (74%)
Treatment-related and severe	9 (10%)	11 (12%)
Leading to mortality	22 (25%)	26 (29%)
Treatment-related and leading to mortality	1 (1%)	1 (1%)
Leading to treatment discontinuation	22 (25%)	29 (33%)
Treatment-related and leading to treatment discontinuation	8 (9%)	5 (6%)
Treatment-related treatment-emergent adverse events known to be associated with sildenafil or pirfenidone		
Gastrointestinal disorder*	14 (16%)	7 (8%)
Photosensitivity or rash†	3 (3%)	6 (7%)
Hepatic side effects‡	0	1 (1%)
Clinically significant vascular event§	4 (5%)	6 (7%)
Hypotension event¶	4 (5%)	6 (7%)

MedDRA version 22.1 was used for coding. Treatment emergent adverse events were defined as adverse events that started or worsened on or after first intake of randomised treatment until last positive dose +28 days. MedDRA=Medical Dictionary for Regulatory Activities. *System organ class gastrointestinal disorders. †MedDRA preferred terms: nodular rash, photodermatosis, photosensitivity reaction, pruritus, pruritus generalised, rash, rash erythematous, rash generalised, rash macular, rash macro-papular, rash papular, rash pruritic, solar dermatitis, solar urticaria, sunburn, erythema, and dry skin. ‡Potential Hy's Law standard adverse event group term. §Sum of ischaemic heart disease, central nervous system vascular disorders, haemorrhages, embolic, and thrombotic events and MedDRA preferred term pulmonary oedema, and vascular hypotensive disorders. ¶MedDRA higher-level term vascular hypotensive disorders.

Table 3: **Treatment-emergent adverse events in the safety population**

to have had a treatment-related treatment-emergent adverse event. Treatment-emergent adverse events leading to sildenafil or placebo discontinuation were reported in 22 (25%) patients in the sildenafil group and 29 (33%) patients in the placebo group. Treatment-emergent adverse events leading to sildenafil or placebo discontinuation are shown in the appendix (p 13). There were 33 deaths during the double-blind treatment period: 15 (17%) in the sildenafil group and 18 (20%) in the placebo group; 14 of these occurred within the first 6 months (seven [8%] in each treatment group). The incidence of treatment-emergent adverse events leading to mortality is shown in table 3.

Discussion

In this phase 2b trial in patients with advanced IPF and intermediate or high probability of group 3 pulmonary hypertension, the addition of sildenafil to pirfenidone did not provide a treatment benefit compared with pirfenidone plus placebo as judged by disease progression and changes in pulmonary function tests, exercise capacity, or health-related quality of life up to 52 weeks. Safety and tolerability were similar between the sildenafil and placebo treatment groups.

Sildenafil has previously been studied in IPF with inconclusive results. The STEP-IPF study[16] evaluated the efficacy and safety of sildenafil monotherapy versus placebo in patients with advanced IPF (percent predicted DLco <35%) up to 12 weeks. Although the primary endpoint was not met, a treatment difference favouring sildenafil versus placebo was observed for changes from baseline in SGRQ and UCSD-SOBQ total scores. The INSTAGE study[21] of nintedanib plus sildenafil versus nintedanib plus placebo in advanced IPF (percent predicted DLco ≤35%) also did not meet its primary endpoint; however, patients in the nintedanib plus sildenafil group were less likely to experience an absolute decline of 5% or more in percent predicted FVC or death than the patients in the nintedanib plus placebo group. It is important to note that both STEP-IPF and INSTAGE selected patients with advanced IPF on the basis of DLco alone, and that risk of pulmonary hypertension was not otherwise assessed. We hypothesised that the use of sildenafil in patients with pulmonary vascular involvement might be a more promising approach and therefore enrolled patients with advanced IPF at risk of having or developing group 3 pulmonary hypertension. The definition of risk of having group 3 pulmonary hypertension (a mean pulmonary arterial pressure ≥20 mm Hg with pulmonary artery wedge pressure ≤15 mm Hg on right-heart catheterisation or intermediate or high probability of group 3 pulmonary hypertension on echocardiography) was chosen on the basis of our hypothesis that sildenafil might have a role in treating patients at risk of poor outcomes due to pulmonary hypertension, whether already present or likely to develop during the trial period. The definition was selected before the new, lower definition of pulmonary hypertension (mean pulmonary arterial pressure ≥20 mm Hg) proposed during the World Symposium on Pulmonary Hypertension in 2018.[22] However, no evidence of a treatment benefit from the early addition of sildenafil to pirfenidone was observed across any of the outcomes assessed in our study. Taken together, these results seem to suggest that sildenafil should not be used routinely in patients with IPF. However, it should be noted that in the Kaplan-Meier analysis, respiratory-related mortality was reduced by approximately 33% in the sildenafil arm versus the placebo arm—a finding that is based on small event numbers but might merit further investigation—and, furthermore, we cannot rule out that there might be a subset of patients who would benefit from treatment.

Although this study did not meet its primary endpoint, there were some valuable findings. The incidence of treatment-emergent adverse events known to be associated with pirfenidone was lower than that in the phase 3 clinical trials,[23] most likely because of the selection bias introduced by the inclusion criterion that patients had to be established on, and tolerating, pirfenidone before entering this study. Data on pirfenidone in advanced IPF are scarce. However, a post-hoc analysis of a subgroup of patients in ASCEND and

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CAPACITY with percent predicted FVC of less than 50% or percent predicted DLco of less than 35%, or both, revealed that patients with advanced disease in the pirfenidone group had similar incidences of common treatment-emergent adverse events and discontinuations due to treatment-emergent adverse events to those in the overall pooled population.[24] Similarly, in a post-hoc analysis of RECAP, the open-label extension study of ASCEND and CAPACITY, the safety profile of pirfenidone was similar in patients with percent predicted FVC of less than 50% or percent predicted DLco of less than 35%, or both, versus patients with FVC of 50% or more or DLco of 35% or more, or both.[25] Furthermore, in a post-marketing safety surveillance study of all patients treated with pirfenidone in the first year after its launch in Japan (n=1371), the rate of discontinuation due to adverse events at 12 months was similar across disease-severity subgroups.[26] However, discontinuations due to disease progression increased with disease severity, and disease severity was classified using different criteria to those used in the current study.[26] Overall, combined with the prospective data collected on safety and tolerability in the current study, the evidence suggests that patients with advanced IPF tolerate pirfenidone treatment.

As highlighted, patients with advanced IPF were largely excluded from the phase 3 trials and efficacy data in this population are scarce. Although our study did not have a true placebo group and cannot be directly compared with the phase 3 data, we can consider our data within the context of existing data on FVC decline in patients with IPF taking pirfenidone. Patients in the pooled ASCEND and CAPACITY population had a mean FVC change over 1 year of –216 mL in the pirfenidone group,[27] and patients in RECAP included from CAPACITY had an annualised rate of FVC decline of –144·3 mL.[28] In addition, in a retrospective real-world study of 43 patients with advanced IPF (percent predicted FVC <50% or percent predicted DLco <35%, or both), initiation of pirfenidone was associated with a trend for reduced FVC decline over 6 months versus the 6 months before treatment initiation, although this benefit was not seen after 1 year.[29] In the current study, mean FVC change from baseline to 52 weeks in the pirfenidone plus placebo group was –93·0 mL. Although the high discontinuation rate in our study and the potential for survival bias should be considered, these results do support the hypothesis that pirfenidone might reduce FVC decline in advanced IPF. The potential benefits of antifibrotics in advanced IPF are further supported by the INSTAGE trial,[21] in which the mean FVC change from baseline at week 24 was –58·2 mL in the nintedanib plus placebo group. Again, although direct comparisons should be avoided, the mean FVC change from baseline at week 24 in the pivotal INPULSIS trial[30] was –52·8 mL (SE 9·8) in the nintedanib group.[30] Although conclusions from our own study are limited by the absence of a true placebo group and further prospective research is clearly required, consideration of all the available evidence together does suggest that patients with advanced disease might also benefit from antifibrotics and supports the need for further investigation.

The design of this study had several strengths. To the best of our knowledge, this was the first trial of sildenafil in the context of IPF to report outcomes up to 52 weeks, as STEP-IPF reported outcomes up to 12 weeks and INSTAGE up to 24 weeks; however, the long study duration in advanced disease was associated with high incidences of mortality and sildenafil or placebo discontinuation, and low patient numbers by the end of the study. Furthermore, although the composite primary endpoint in our study had several limitations, it did provide additional value versus previous trials of sildenafil in IPF that did not include hard outcomes (which are definitive to the disease process and require no subjectivity) as part of their primary endpoints.[14–16] In addition, the distribution of events was in line with similarly constructed endpoints used in pulmonary arterial hypertension trials, further attesting to the potential usefulness of our composite endpoint in this patient population. The eligibility criteria were another strength, enabling inclusion of patients at risk of pulmonary vascular disease, in the absence of right-heart catheterisation-proven pulmonary hypertension. Although right-heart catheterisation is often stated to be the gold standard method for the diagnosis of pulmonary hypertension, echocardiography is the most widely used non-invasive diagnostic tool for the assessment of group 3 pulmonary hypertension and is recommended in the European Society of Cardiology and European Respiratory Society guidelines.[7] Furthermore, because our aim was to investigate the effect of sildenafil in patients at risk of poor outcomes due to pulmonary hypertension regardless of whether pulmonary hypertension was already present or was likely to develop, the low proportion of patients with previous right-heart catheterisation should not be considered a weakness of this study. Furthermore, the guidelines advise that right-heart catheterisation in group 3 pulmonary hypertension is only recommended if organ transplant is considered, if there is suspected pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, if there are episodes of right ventricular failure, or if the echocardiography results were inconclusive in cases with a high level of suspicion of pulmonary hypertension and potential therapeutic implications.[7]

There were some weaknesses regarding the design of this study. Possible limitations included the absence of a placebo-only treatment group, preventing robust conclusions regarding the efficacy and safety of pirfenidone monotherapy in advanced IPF. Selection bias must also be considered. For example, the longer duration of previous pirfenidone treatment in the placebo group versus the sildenafil group could have meant that patients in the placebo group were a more stable group who were less predisposed to progression.

Furthermore, considering that patients in the placebo group had a longer duration of disease, this also supports the argument that they might have had a greater predisposition to stability. It should also be noted that patients in the placebo group had slightly more severe disease at baseline versus the sildenafil group, which might have masked worse outcomes in the sildenafil group, and might explain why a higher number of patients discontinued from double-blind treatment in the placebo group versus the sildenafil group. Although the use of a composite primary endpoint that included all-cause mortality was a strength of this study, it should also be acknowledged that because of the absence of a treatment difference observed for all-cause mortality, the composite endpoint could also be considered as a limitation.

In conclusion, combination therapy with pirfenidone plus sildenafil did not provide a clinically meaningful benefit compared with pirfenidone plus placebo in patients with advanced IPF and intermediate or high probability of group 3 pulmonary hypertension. Although the absence of a beneficial treatment effect suggests that sildenafil is not an appropriate treatment in the overall population, further research is required to establish if specific subgroups of patients might benefit from sildenafil. No new safety signals were identified with either treatment and the safety profiles were similar in both treatment groups.

Contributors

All authors were involved in the conception or design of the work, or both, and in the interpretation of the study results. All authors contributed to the manuscript from the outset, and read and approved the final draft. All authors vouch for the accuracy of the content included in the final manuscript.

Declaration of interests

JB has received personal fees for lectures and consulting services from Actelion, Boehringer Ingelheim, F Hoffmann-La Roche, Pliant, Promedior (a subsidiary of F Hoffmann-La Roche), MSD, Bristol-Myers Squibb, Novartis, AstraZeneca, and Galapagos, outside of the submitted work; and is a member of national and international guideline committees for idiopathic pulmonary fibrosis (IPF). SDN is a consultant and is on the speakers' bureau for Boehringer Ingelheim and F Hoffmann-La Roche; is also a consultant for Bellerophon, and United Therapeutics; and his institution has received research funding from Boehringer Ingelheim and F Hoffmann-La Roche, all outside of the submitted work. WAW has received consulting fees and lecture fees from Boehringer Ingelheim and F Hoffmann-La Roche, paid to his institution, outside of the submitted work. NMB has received lecture fees from Actelion, Boehringer Ingelheim, and F Hoffmann-La Roche, outside of the submitted work. DEB has received personal fees for lectures and consulting services from Boehringer Ingelheim and F Hoffmann-La Roche; his institution has received research funding from Boehringer Ingelheim and F Hoffmann-La Roche, all outside of the submitted work; and he is a member of international guideline committees for IPF. KA has received consulting and lecture fees from Boehringer Ingelheim, F Hoffmann-La Roche, GlaxoSmithKline, and Menarini; her institution has received sponsorship and research funding from Boehringer Ingelheim and F Hoffmann-La Roche, all outside of the submitted work. JG has received consulting and lecture fees from Actelion, Boehringer Ingelheim, F Hoffmann-La Roche, and GlaxoSmithKline; his institution has received research fees from Actelion, Boehringer Ingelheim, and F Hoffmann-La Roche, all outside of the submitted work. K-UK and MB are employees and shareholders of F Hoffmann-La Roche. FG and AP are employees of F Hoffmann-La Roche. SH has served as a consultant for, received speakers' bureau fees from, and received research funding from Actelion, Boehringer Ingelheim, and F Hoffmann-La Roche, outside of the submitted work. AUW has received consulting and lecture fees from Boehringer Ingelheim, F Hoffmann-La Roche, and Blade Therapeutics, outside of the submitted work. MRK declares no competing interests.

Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org). Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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