Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

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Summary

Background At present, no approved pharmacotherapies are available for unclassifiable interstitial lung disease (ILD), which is characterised by progressive fibrosis of the lung. We aimed to assess the efficacy and safety of pirfenidone in patients with progressive fibrosing unclassifiable ILD.

Methods We did a multicentre, double-blind, randomised, placebo-controlled phase 2 trial at 70 centres in Australia, Belgium, Canada, Czech Republic, Denmark, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Spain, and the UK. Eligible patients (aged ≥18–85 years) had progressive fibrosing unclassifiable ILD, a percent predicted forced vital capacity (FVC) of 45% or higher and percent predicted carbon monoxide diffusing capacity (DLco) of 30% or higher, more than 10% fibrosis on high-resolution CT, and a high-resolution CT from the previous 12 months. Patients were randomly assigned (1:1) to 2403 mg oral pirfenidone daily or placebo using a central validated interactive voice or web-based response system, stratified by concomitant mycophenolate mofetil use and presence or absence of interstitial pneumonia with autoimmune features. Investigators, site personnel, and patients were masked to treatment assignment. The primary endpoint was mean predicted change in FVC from baseline over 24 weeks, measured by daily home spirometry. Secondary endpoints were change in FVC measured by site spirometry, proportion of patients who had a more than 5% or more than 10% absolute or relative decline in percent predicted FVC measured by clinic-based spirometry, change in percent predicted DLco, change in 6-min walk distance (6MWD), change in University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ) score, change in Leicester Cough Questionnaire score, change in cough visual analogue scale, and changes in total and subscores of the St George's Respiratory Questionnaire (SGRQ), all of which were compared with baseline. Additional secondary endpoints included proportion of patients who had non-elective hospitalisation (respiratory and all-cause) and acute exacerbations, and progression-free survival. Efficacy was analysed in the intention-to-treat (ITT) population, which included all randomly assigned patients. Safety was assessed in the safety analysis set, which included all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03099187, and is no longer recruiting.

Findings Between May 15, 2017, and June 5, 2018, 253 patients were randomly assigned to receive 2403 mg pirfenidone (n=127) or placebo (n=126) and were included in the ITT analysis set. Analysis of the primary endpoint was affected by intraindividual variability in home spirometry values, which prevented application of the prespecified statistical model. Over 24 weeks, predicted median change in FVC measured by home spirometry was –87·7 mL (Q1–Q3 –338·1 to 148·6) in the pirfenidone group versus –157·1 mL (–370·9 to 70·1) in the placebo group. Over 24 weeks, predicted mean change in FVC measured by site spirometry was lower in patients given pirfenidone than placebo (treatment difference 95·3 mL [95% CI 35·9 to 154·6], p=0·002). Compared with the placebo group, patients in the pirfenidone group were less likely to have a decline in FVC of more than 5% (odds ratio [OR] 0·42 [95% CI 0·25 to 0·69], p=0·001) or more than 10% (OR 0·44 [0·23 to 0·84], p=0·011). At week 24, mean change in DLco from baseline was –0·7% (SD 7·1) for the pirfenidone group and –2·5% (8·8) for the placebo group, and mean change in 6MWD from baseline was –2·0 m (68·1) for the pirfenidone group and –26·7 m (79·3) for the placebo group. Changes from baseline in UCSD-SOBQ, Leicester Cough Questionnaire score, cough visual analogue scale, and SGRQ scores were similar between the pirfenidone and placebo groups at week 24. Analysis of acute exacerbations, hospital admissions, and time to death from respiratory causes during the study yielded no meaningful results due to a small number of events. No differences in progression-free survival were identified between the pirfenidone and placebo groups, irrespective of the definition of progression-free survival used. Treatment-emergent adverse events were reported in 120 (94%) of 127 patients in the pirfenidone group and 101 (81%) of 124 patients in the placebo group. Serious treatment-emergent adverse events were reported in 18 (14%) patients in the pirfenidone group and 20 (16%) patients in the placebo group. The most common treatment-related treatment-emergent adverse events were gastrointestinal disorders (60 [47%] in the pirfenidone group *vs* 32 [26%] in the placebo group), fatigue (16 [13%] *vs* 12 [10%]), and rash (13 [10%] *vs* nine [7%]).

Interpretation Although the planned statistical model could not be applied to the primary endpoint data, analysis of key secondary endpoints suggests that patients with progressive fibrosing unclassifiable ILD could benefit from

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pirfenidone treatment, which has an acceptable safety and tolerability profile. These findings support further investigation of pirfenidone as an effective treatment for patients with progressive fibrotic unclassifiable ILD.

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Introduction

Interstitial lung diseases (ILDs) are a large, heterogeneous group of diseases characterised by abnormalities of the pulmonary interstitium or alveoli, including fibrosis.[1] Patients with ILD have difficulty with daily activities, shortness of breath, tiredness, and fatigue.[2] ILDs might be associated with environmental exposures or can be secondary to another condition, such as a connective tissue disease, but in many cases, a cause is not established, and these patients are diagnosed with idiopathic interstitial pneumonias.[1]

Although some ILDs have a progressive fibrosing phenotype similar to idiopathic pulmonary fibrosis (IPF), which is the most common form of idiopathic interstitial pneumonia,[3] the clinical course of other ILDs varies.[1,4,5] Diagnosis of a specific ILD is important for identifying the most appropriate management strategy and informing disease prognosis.[1,4,5] However, as recognised by American Thoracic Society/European Respiratory Society diagnostic guidelines for idiopathic interstitial pneumonia,[6] despite thorough investigation by a multidisciplinary team (including pulmonologists, radiologists, and lung pathologists), a final diagnosis is not always possible,[4] subsequently leading to a diagnosis of unclassifiable ILD.[7]

The management of patients with ILD is divided into two categories: patients with IPF and patients with all other progressive forms of fibrotic ILD. For IPF, two antifibrotic drugs are available—pirfenidone and nintedanib—which have been shown to slow disease progression.[8–10] In the absence of clinical evidence guiding the treatment of other fibrosing ILDs (eg, unclassifiable ILD, hypersensitivity pneumonitis, connective tissue disease ILD), options include treatment with short-term

Research in context

Evidence before this study

We searched PubMed from database inception to May 31, 2019, for reports published in any language using the search terms ("uILD" OR "unclassifiable interstitial lung disease" OR "unclassifiable ILD" OR ("unclassifiable" AND ("interstitial lung disease" OR "ILD"))), which yielded 57 articles. After excluding publications that were not in English or not related to unclassifiable interstitial lung disease (ILD), 48 articles remained. To focus on the treatment of unclassifiable ILD, we then excluded case studies and articles on prevalence or incidence, diagnosis, disease classification, natural history, or prognosis, which left 11 articles. To focus on pharmacological treatments, we excluded two articles investigating lung transplant as a treatment for unclassifiable ILD. Of the remaining articles, seven were review articles or opinion pieces, one was a retrospective review of medical records that included only three patients with unclassifiable ILD, and one was a study design manuscript. Thus, our search identified no randomised controlled trials investigating a pharmacological treatment in patients with unclassifiable ILD.

Added value of this study

To our knowledge, this is the first randomised controlled trial to exclusively enrol patients with unclassifiable ILD, a type of ILD for which no approved pharmacological treatments exist. Pirfenidone is an antifibrotic shown to slow disease progression in patients with idiopathic pulmonary fibrosis (IPF), a form of ILD that has mechanistic and clinical similarities with progressive fibrotic unclassifiable ILD. This study investigated the efficacy and safety of pirfenidone compared with placebo over 24 weeks of treatment in patients with progressive fibrotic unclassifiable ILD. As a result of unanticipated technical and analytical issues with home spirometry, it was not possible to apply the planned statistical model to the primary endpoint data. However, analysis of key secondary and exploratory endpoints measured at site visits, including forced vital capacity, carbon monoxide diffusing capacity, and 6-min walk distance, suggested that, compared with placebo, 24 weeks of treatment with pirfenidone is effective in patients with progressive fibrosing unclassifiable ILD. The safety and tolerability profile of pirfenidone was comparable with that observed in the phase 3 trials in IPF, and no new safety signals were identified.

Implications of all the available evidence

At present, no direct evidence to guide the treatment of patients with unclassifiable ILD exists and no approved pharmacological treatments are available; therefore, the results of this study are important for patients with progressive fibrosing unclassifiable ILD and clinicians involved in their treatment. This study found that pirfenidone was associated with benefits in lung function and exercise capacity compared with placebo after 24 weeks of treatment, thus supporting future studies investigating the benefits of pirfenidone in this patient population over a longer time period. Furthermore, the technical and analytical issues encountered with home spirometry in this study also have important implications for the design of future clinical trials. Thus, further analyses are needed before daily home spirometry can be used as a primary outcome measure in future clinical trials.

immunosuppression followed by an evaluation of treatment response, or continued observation without pharmacotherapy.[3,5,11]

Although these treatments can be used in practice, at present, no approved treatments are available for unclassifiable ILD.[12] Considering the mechanistic and clinical similarities between IPF and other ILDs with a progressive fibrosing phenotype, it is reasonable to hypothesise that antifibrotics might be beneficial in patients with progressive unclassifiable ILDs characterised by fibrosis.[12,13]

We aimed to assess the efficacy and safety of pirfenidone versus placebo in patients with progressive fibrosing unclassifiable ILD over 24 weeks of treatment.[12]

Methods

Study design and participants

We did a multicentre, double-blind, randomised, placebo-controlled phase 2 trial at 70 clinical centres in Australia, Belgium, Canada, Czech Republic, Denmark, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Spain, and the UK. The methods of this study have been previously described.[12]

Eligible patients were aged between 18 and 85 years and had fibrosing unclassifiable ILD, defined as fibrosing ILD that could not be classified with moderate or high confidence to any category of ILD after multidisciplinary team discussion at each centre. Patients who had a percent predicted forced vital capacity (FVC) of 45% or higher and percent predicted carbon monoxide diffusing capacity (DLco) of 30% or higher, more than 10% fibrosis on high-resolution CT, and a high-resolution CT from the previous 12 months were included. Patients were also required to have a FEV_1/FVC ratio of 0·7 or higher, a 6-min walking distance (6MWD) of 150 m or higher, and progressive disease, defined as either a more than 5% absolute decline in percent predicted FVC[14] or significant symptomatic worsening not due to cardiac, pulmonary (except worsening of underlying unclassifiable ILD), vascular, or other causes (as determined by the investigator) within the previous 6 months. Exclusion criteria have been previously described.[12]

The trial was done in accordance with the ethical principles of the Good Clinical Practice guidelines and the Declaration of Helsinki, and local laws for countries in which the research was done. Informed consent was obtained from each participant by the study investigator before any study-specific screening procedures were done.

Randomisation and masking

After a screening period of up to 21 days, eligible patients were randomly assigned (1:1) to receive 2403 mg oral pirfenidone daily or placebo for 24 weeks. Randomisation was done using a central validated interactive voice or web-based response system hosted by Bracket Global (San Francisco, CA, USA) using permuted block randomisation (block size four). Randomisation was stratified by concomitant mycophenolate mofetil use and presence or absence of interstitial pneumonia with autoimmune features.[15] Investigational and site personnel and patients were masked to treatment assignment. To maintain masking of the treatment group to investigators, study participants, and the funder, study participants randomly assigned to the placebo group were administered placebo capsules with identical appearance, size, and taste to pirfenidone capsules. Unmasking was only permitted in emergency situations, such as the occurrence of a serious adverse event, when the study investigator would be permitted to determine a patient's allocated intervention by contacting Bracket Global. Maintenance of masking was continually assessed by the study coordinator at each investigational site. The database was locked until statistical analysis.

Procedures

During screening, patients were evaluated for eligibility on the basis of the inclusion and exclusion criteria. At the screening visit, patients were given a 60-min session on how to use the spirometer. The full schedule of assessments done at the screening visit and at each site visit during the study is available in the appendix (pp 2–6). See Online for appendix

All interventions were given orally. Patients were instructed to take three placebo or 267 mg pirfenidone capsules three times daily for 24 weeks. Patients were instructed to take a single spirometry reading using a portable handheld Micro spirometer (Vyaire Medical, Basingstoke, UK) at approximately the same time each day. Blows were categorised by a spirometer-based algorithm as rejected, borderline accepted, or accepted, with only accepted manoeuvres retained for analysis. Blows that were shorter than 6 s but had a flow change of 100 mL in the last 0·5 s were classified as acceptable blows. These criteria were recommended by the device manufacturer and enabled the capture of data that would have been discarded using site spirometry. Coughing during the blow rendered a warning message of bad blow, which allowed the patient to take a repeat reading on the same day. Patients were masked to daily spirometry values. Refresher training on the use of spirometers was offered after month 1, between months 2 and 3, and between months 4 and 5. Efficacy outcomes and safety outcomes were assessed at scheduled study visits every 4 weeks during the 24-week treatment period (appendix pp 2–6). Spirometer data were downloaded by site staff at each site visit. Safety and tolerability of pirfenidone was also assessed until approximately 28 days after patients received their last dose of study drug taken during the double-blind treatment period.

Outcomes

The primary endpoint was predicted mean change in FVC from baseline over 24 weeks, measured by daily home spirometry.

Secondary endpoints were change in FVC from baseline, measured by spirometry during clinic visits; proportion of patients who had a more than 5% or more than 10% absolute or relative decline in percent predicted FVC measured by site spirometry; change in percent predicted DLco from baseline; change in 6MWD from baseline; change in University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ) score from baseline; change in Leicester Cough Questionnaire score from baseline; change in cough visual analogue scale from baseline; change in the St George's Respiratory Questionnaire (SGRQ) total and subscores from baseline; the proportion of patients who had all-cause and respiratory non-elective hospital admission; the incidence of, and time to first, investigator-reported acute exacerbation; progression-free survival, defined as time to first occurrence of more than a 10% absolute decline in percent predicted FVC (clinic-based spirometry), a more than 50 m decline in 6MWD, or death, or alternatively defined as time to first occurrence of a more than 10% relative decline in percent predicted FVC, non-elective respiratory hospital admission, or death; and time to death from respiratory causes.

Prespecified exploratory endpoints were the proportion of patients with more than a 15% absolute decline in percent predicted DLco and the proportion of patients with more than a 50 m decline in 6MWD. We also did a prespecified subgroup analysis of mean change in FVC from baseline to week 24 measured using site spirometry to assess treatment response in subgroups stratified by age, sex, lung function, weight, mycophenolate mofetil treatment, and the presence or absence of interstitial pneumonia with autoimmune features.

The incidence and severity of treatment-emergent adverse events and withdrawals from study treatment or study discontinuations were recorded. The incidence, type, and severity of adverse events were summarised according to primary System Organ Class and subcategorised by Medical Dictionary for Regulatory Activities preferred terms (version 19.1).

Statistical analysis

We estimated that 250 patients (125 in each group) would be needed to assess the primary endpoint, assuming 80% power and a two-sided significance level of 5% using a Student's *t* test. On the basis of historical data, we assumed that FVC decline would be 85 mL (SD 70) in the placebo group and 60 mL (70) in the pirfenidone group. On the basis of this assumption, a sample size of 125 patients per treatment group would be needed to detect this treatment effect at the 5% significance level with 80% power.[12] The median doses of pirfenidone and placebo were summarised descriptively. The median number of placebo capsules was translated into a theoretical pirfenidone dose—eg, nine placebo capsules was equivalent to 2403 mg pirfenidone per day. Primary and secondary efficacy endpoints were assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients. For the prespecified primary endpoint analysis, we planned to calculate estimated FVC change for each individual patient by applying a linear regression model to available daily home spirometry measurements collected during the 24-week treatment period. We planned to compare the mean change in FVC predicted from these linear models at 24 weeks between treatment groups using a Student's *t* test with a two-sided significance level of 5%. However, data for each treatment group were assessed using the Shapiro-Wilks test of normality, which suggested that the statistical assumptions for applying a Student's *t* test were not fulfilled and thus, the planned statistical model could not be applied to the primary endpoint data. We did not consider the use of a non-parametric test because such tests would be unable to estimate a difference between the two treatment groups in predicted FVC decline at 24 weeks—ie, rank analysis of covariance (ANCOVA) would only consider the last observed FVC values and all other daily measurements would be disregarded. Therefore, we have presented the primary endpoint data descriptively, and have selected the median as the most appropriate statistic considering the skewed data distribution, since this parameter is less affected by outliers. Patients who discontinued treatment prematurely were analysed based on all available data, and no imputation method was applied for missing data (ie, we did not use an algorithm to calculate values beyond the discontinuation date of a patient).

For the secondary efficacy endpoints, all data from baseline to week 24 were used without imputation of values for patients who discontinued early. p values were reported with no adjustment for multiplicity and are for descriptive purposes only. The predicted change in FVC between baseline and week 24 measured by site spirometry was compared between the treatment groups using the same method as that for the primary endpoint. Changes in percent predicted FVC and percent predicted DLco were compared between treatment groups using a rank ANCOVA model, with change from baseline used as an outcome variable and standardised rank baseline value used as covariate. Categorical changes in percent predicted FVC (>5% and >10%) were compared between treatment groups using a Cochran-Mantel-Haenszel test. Changes in 6MWD, UCSD-SOBQ, Leicester Cough Questionnaire, cough visual analogue scale, and total and subscores of the SGRQ were analysed using a rank ANCOVA model, with the recorded value at 24 weeks used as an outcome variable and the standardised rank baseline value used as a covariate. All-cause and respiratory non-elective hospitalisation, progression-free survival, and time to death from any cause were analysed using Kaplan–Meier, and the two treatment groups were compared with a log rank test; hazard ratios (HR) and corresponding 95% CIs were calculated by applying Cox proportional hazard models. The incidence of investigator-reported acute

exacerbations in the two treatment groups were compared with Fisher's exact test.[12]

For the prespecified exploratory endpoints, categorical changes in percent predicted DLco (>15%) and 6MWD (>50 m) were compared between treatment groups using logistic regression. For the subgroup analysis of FVC change measured using site spirometry, patients were stratified into subgroups based on age, sex, lung function, weight, mycophenolate mofetil treatment, and the presence or absence of interstitial pneumonia with autoimmune features, with mean change in FVC calculated as described previously.

Safety was analysed in the safety analysis set, which included all randomly assigned patients who received at least one dose of study drug. An independent data monitoring committee reviewed the safety data and advised on trial conduct a minimum of three times during the trial. All statistical analyses were done using SAS (version 9.4).

This study is registered with ClinicalTrials.gov, NCT03099187.

Role of the funding source

The funder designed the study and was involved in data interpretation, data analysis, and the writing of the manuscript, in collaboration with the academic authors. 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 May 15, 2017, and June 5, 2018, 253 patients were randomly assigned to receive pirfenidone (n=127) or placebo (n=126). Two patients in the placebo group did not receive treatment due to randomisation errors. 253 patients were included in the ITT analysis set (127 patients in the pirfenidone group and 126 patients in the placebo group; figure 1) and all randomly assigned patients who received at least one dose of study drug were included in the safety population (127 patients in the pirfenidone group and 124 patients in the placebo group).

Baseline characteristics were similar between the treatment groups (table 1). Most patients in the pirfenidone and placebo groups had a diagnosis of unclassifiable ILD without any features suggestive of another form of ILD (table 1).

The median daily dose was 2281·62 mg per day (Q1–Q3 1886·08–2302·28) for pirfenidone and 2299·80 mg per day (2254·57–2302·88) for placebo. Mean treatment duration, excluding dose interruptions, was 20·7 weeks (SD 6·8) for the pirfenidone group and 22·8 weeks (4·7) for the placebo group. Mean treatment durations for pirfenidone and placebo remained similar when dose interruptions were included.

Analysis of the primary endpoint, as prespecified in the statistical analysis plan, was impossible due to two issues with the recorded home spirometry values: the recorded readings were affected by issues with technical reliability and the application of a linear regression model was not suitable in patients with a small number of readings collected within a short time period. The values obtained were physiologically implausible (daily home FVC values of <0·5 L or >6 L and predicted increases in FVC of 33 L at 24 weeks). These outliers meant that the planned statistical model could not be applied to the primary endpoint data, because the statistical assumptions (continuous data with independent observations in each sample that are normally distributed with equal variance) for applying a Student's *t* test were not fulfilled. At 24 weeks, the mean predicted change in FVC from baseline was –17·9 mL (range –5799 to 16 411) in the pirfenidone group and 116·6 mL (–7256 to 33 794) in the placebo group. At 24 weeks, the median predicted change in FVC from baseline measured by daily home spirometry was –87·7 mL (Q1–Q3 –338·1 to 148·6) in the pirfenidone group and –157·1 mL (–370·9 to 70·1) in the placebo group (figure 2).

The statistical assumptions for applying a Student's *t* test were met when applied to secondary endpoints. At

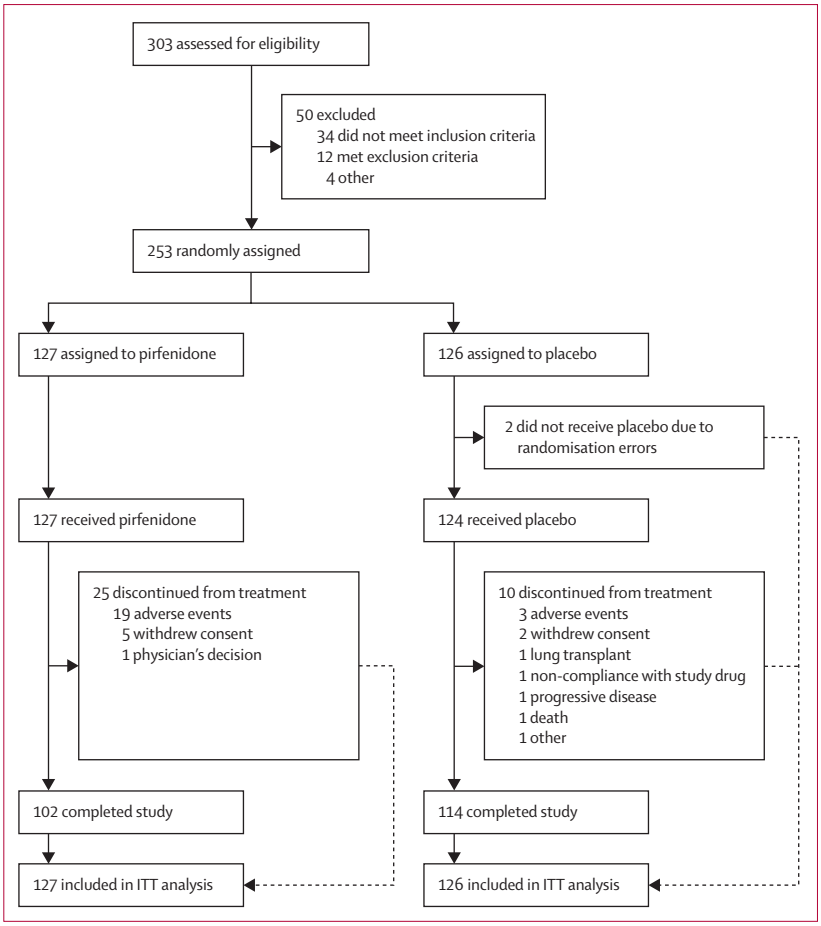

Figure 1: **Trial profile**
AE=adverse event. ITT=intention-to-treat.

	Pirfenidone (n=127)	Placebo (n=126)
Age at screening, years	70·0 (61·0–76·0)	69·0 (63·0–74·0)
Sex		
Men	70 (55%)	69 (55%)
Women	57 (45%)	57 (45%)
Race		
White	120 (94%)	123 (98%)
Black	1 (1%)	2 (2%)
Asian	5 (4%)	0
Native American or Alaskan Native	1 (1%)	0
Other	0	1 (1%)
Body-mass index, kg/m²	28·6 (26·5–32·9)	29·3 (26·2–32·7)
Previous surgical lung biopsy	40 (31%)	48 (38%)
Percent predicted FVC	71·0% (59·0–87·3)	71·5% (58·0–88·0)
Percent predicted DLco	44·6% (36·9–53·5)	48·0% (38·4–59·0)
Percent predicted FEV_1	75·0% (62·0–88·0)	76·0% (62·0–92·7)
FEV_1/FVC ratio	0·82 (0·78–0·86)	0·84 (0·78–0·87)
6MWD, m	372·0 (303·0–487·0)	395·0 (325·0–472·0)
Concomitant treatment with mycophenolate mofetil	23 (18%)	22 (17%)
IPAF diagnosis	15 (12%)	18 (14%)
Concomitant treatment with mycophenolate mofetil	6 (5%)	6 (5%)
Unclassifiable ILD diagnosis		
Low-confidence rheumatoid arthritis-ILD	0	0
Low-confidence systemic sclerosis-ILD	0	1 (1%)
Low-confidence undifferentiated connective tissue disease-ILD	3 (2%)	2 (2%)
Low-confidence chronic hypersensitivity pneumonitis-ILD	10 (8%)	9 (7%)
Low-confidence idiopathic non-specific interstitial pneumonia-ILD	4 (3%)	3 (2%)
Low-confidence sarcoidosis-ILD	0	0
Low-confidence myositis-ILD	0	0
Low-confidence other defined ILD	1 (1%)	0
Unclassifiable ILD	93 (73%)	93 (74%)

Data are median (Q1–Q3) or n (%), unless otherwise specified. The sum of some percentages does not equal 100% because of rounding. 6MWD=6-min walk distance. DLco=carbon monoxide diffusing capacity. FVC=forced vital capacity. ILD=interstitial lung disease. IPAF=interstitial pneumonia with autoimmune features.

Table 1: **Demographic and baseline characteristics of the intention-to-treat population (n=253)**

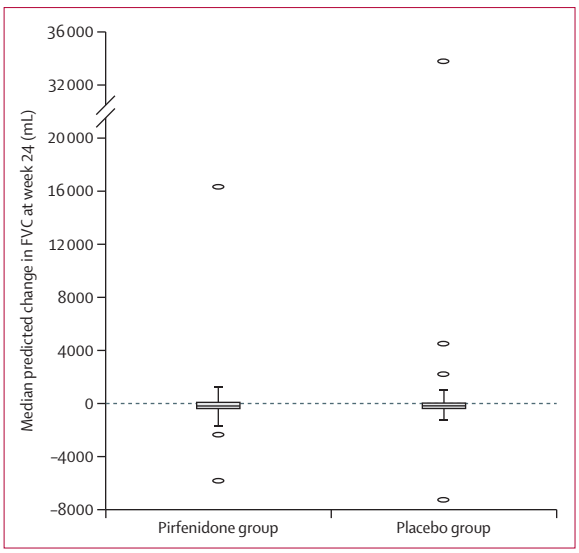

Figure 2: **Median predicted FVC change from baseline at week 24 measured using daily home spirometry in the ITT analysis set (n=253)**
The median change in FVC from baseline was –87·7 mL (Q1–Q3 –338·1 to 148·6) in the pirfenidone group and –157·1 mL (–370·9 to 70·1) in the placebo group. Horizontal lines within the rectangle show the median; the outer lines of the rectangle show the Q1 and Q3 values; the whiskers show the minimum and maximum values, excluding outliers; and circles show the outliers. FVC=forced vital capacity. ITT=intention-to-treat.

week 24, among patients with a baseline measurement and at least two post-baseline measurements (118 patients in the pirfenidone group and 119 patients in the placebo group), mean decline in FVC was lower in patients in the pirfenidone group than patients in the placebo group (–17·8 mL *vs* –113·0 mL; between-group difference 95·3 mL [95% CI 35·9 to 154·6], p=0·002; table 2).

Fewer patients in the pirfenidone group than the placebo group had an absolute decline in percent predicted FVC of more than 5% (47 [37%] of 127 patients in the pirfenidone group *vs* 74 [59%] of 126 patients in the placebo group; odds ratio [OR] 0·42 [95% CI 0·25 to 0·69], p=0·001) and a more than 10% absolute decline in percent predicted FVC (18 [14%] *vs* 34 [27%]; OR 0·44 [0·23 to 0·84], p=0·011; table 2). A relative decline in percent predicted FVC of more than 5% was reported less frequently in patients treated with pirfenidone than placebo (66 [52%] of 127 patients in the pirfenidone group *vs* 84 [67%] of 126 patients in the placebo group; OR 0·55 [0·33 to 0·91], p=0·018); however, no treatment difference was observed for a more than 10% relative decline in percent predicted FVC (36 [28%] *vs* 49 [39%]; OR 0·62 [0·37 to 1·05], p=0·08). Rank ANCOVA analysis for absolute change in percent predicted FVC from baseline to last observed measurement favoured pirfenidone (p=0·038).

Among patients who had available DLco and 6MWD data at week 24, the mean change in percent predicted DLco from baseline was –0·7% (SD 7·1) for the pirfenidone group (n=97) and –2·5% (8·8) for the placebo group (n=110) and the mean change in 6MWD from baseline was –2·0 m (SD 68·1) for the pirfenidone group (n=99) and –26·7 m (79·3) for the placebo group (n=108; table 3). Rank ANCOVA models for change in percent predicted DLco and 6MWD from baseline to last observed measurement yielded p values of 0·09 and 0·040, respectively.

Time-to-event analyses for progression-free survival, defined as more than 10% absolute decline in percent predicted FVC, more than 50 m decline in 6MWD, or death (HR 0·84 [95% CI 0·56 to 1·24]), or defined as more than 10% relative decline in percent predicted FVC, non-elective respiratory hospitalisation, or death (HR 0·79 [0·52 to 1·20]), are presented in the appendix (p 10). No differences in progression-free survival were identified between the pirfenidone and placebo groups, irrespective of the definition used.

	Pirfenidone (n=127)	Placebo (n=126)	Pirfenidone *vs* placebo	p value*
Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	–17·8† (–62·6 to 27·0)	–113·0‡ (–152·5 to –73·6)	95·3 (35·9 to 154·6)	0·002
Median (Q1–Q3)	–7·5 (–185·4 to 112·3)	–125·8 (–238·2 to 2·2)	118·3	..
FVC change from baseline measured by site spirometry, % predicted				
Rank analysis of covariance	..	..	..	0·038
Patients with >5% decline in FVC	47 (37%)	74 (59%)	0·42 (0·25 to 0·69)§	0·001
Patients with >10% decline in FVC	18 (14%)	34 (27%)	0·44 (0·23 to 0·84)§	0·011
DLco change from baseline, % predicted				
Rank analysis of covariance	..	..	..	0·09
Patients with >15% decline in DLco¶	3 (2%)	11 (9%)	0·25 (0·07 to 0·93)§	0·039
6MWD change from baseline, m				
Rank analysis of covariance	..	..	..	0·040
Patients with >50 m decline in 6MWD¶	36 (28%)	35 (28%)	1·03 (0·59 to 1·78)§	0·92

Data are n (%), unless otherwise specified. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *p values for secondary endpoints are not adjusted for multiplicity and are provided for descriptive purposes only. †n=118; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. ‡n=119; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. §Odds ratio (95% CI). ¶Prespecified exploratory outcome.

Table 2: **Secondary and prespecified exploratory outcomes at week 24 in the intention-to-treat population (n=253)**

Changes in UCSD-SOBQ, Leicester Cough Questionnaire, SGRQ, and cough visual analogue scale scores were similar between the pirfenidone and placebo groups (appendix pp 7–8).

Analysis of acute exacerbations, hospital admissions, and time to death from respiratory causes during the study period yielded no meaningful results due to the small number of events.

Three (2%) of 127 patients in the pirfenidone group and 11 (9%) of 126 patients in the placebo group had a more than 15% absolute decline in percent predicted DLco (OR 0·25 [95% CI 0·07 to 0·93], p=0·039). 36 (28%) of 127 patients in the pirfenidone group and 35 (28%) of 126 patients in the placebo group had a more than 50 m decline in 6MWD (OR 1·03 [0·59 to 1·78], p=0·92; table 2).

In an exploratory prespecified subgroup analysis of mean change in FVC from baseline to week 24 measured using site spirometry, a treatment benefit was generally observed with pirfenidone regardless of age, sex, lung function, and presence or absence of interstitial pneumonia with autoimmune features. Subgroup analyses stratified by bodyweight and mycophenolate mofetil treatment seemed to suggest a differential treatment effect, but the small sample sizes prevented meaningful interpretation of these data (figure 3).

Treatment-emergent adverse events were reported in 120 (94%) of 127 patients in the pirfenidone group and 101 (81%) of 124 patients in the placebo group (table 4). 90 (71%) patients in the pirfendone group and 57 (46%) patients in the placebo group reported treatment-emergent adverse events that were deemed to be treatment-related. Serious treatment-emergent adverse events were reported in 18 (14%) patients in the pirfenidone group and 20 (16%) patients in the placebo group. The proportion of patients with adverse reactions known to be associated with pirfenidone (treatment-related photosensitivity, rash, weight decrease, and fatigue) was similar between the treatment groups (<10% difference); however, treatment-related gastrointestinal disorders were more frequent with pirfenidone than placebo (60 [47%] *vs* 32 [26%]). No new safety signals associated with pirfenidone were identified. 19 (15%) patients in the pirfenidone group and five (4%) patients in the placebo group had a treatment-emergent adverse event that led to treatment discontinuation. During the study period, two deaths were reported (one in each

	Pirfenidone (n=127)	Placebo (n=126)
Change in FVC from baseline measured by site spirometry		
Mean, mL	20·0* (7·6)	–80·0† (7·6)
Median, mL	0·0 (–160·0 to 120·0)	–90·0 (–210·0 to 30·0)
Mean, % predicted	–0·4%* (6·9)	–2·5%† (9·2)
Median, % predicted	0·0% (–4·8 to 4·0)	–2·0% (–7·0 to 1·5)
Change in percent predicted DLco from baseline		
Mean	–0·7%‡ (7·1)	–2·5%§ (8·8)
Median	–1·0% (–4·1 to 3·2)	–2·0% (–6·0 to 1·7)
Change in 6MWD from baseline		
Mean, m	–2·0¶ (68·1)	–26·7‖ (79·3)
Median, m	0·0 (–39·0 to 40·0)	–12·0 (–53·5 to 10·5)

Data are mean (SD) or median (Q1–Q3). For some of the analyses, only patients with data available for the relevant outcome measure at week 24 were included, thus patient numbers vary from that included in the intention-to-treat population. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *n=101. †n=112. ‡n=97. §n=110. ¶n=99. ‖n=108.

Table 3: **Descriptive secondary outcome variables at week 24 in the intention-to-treat population (n=253)**

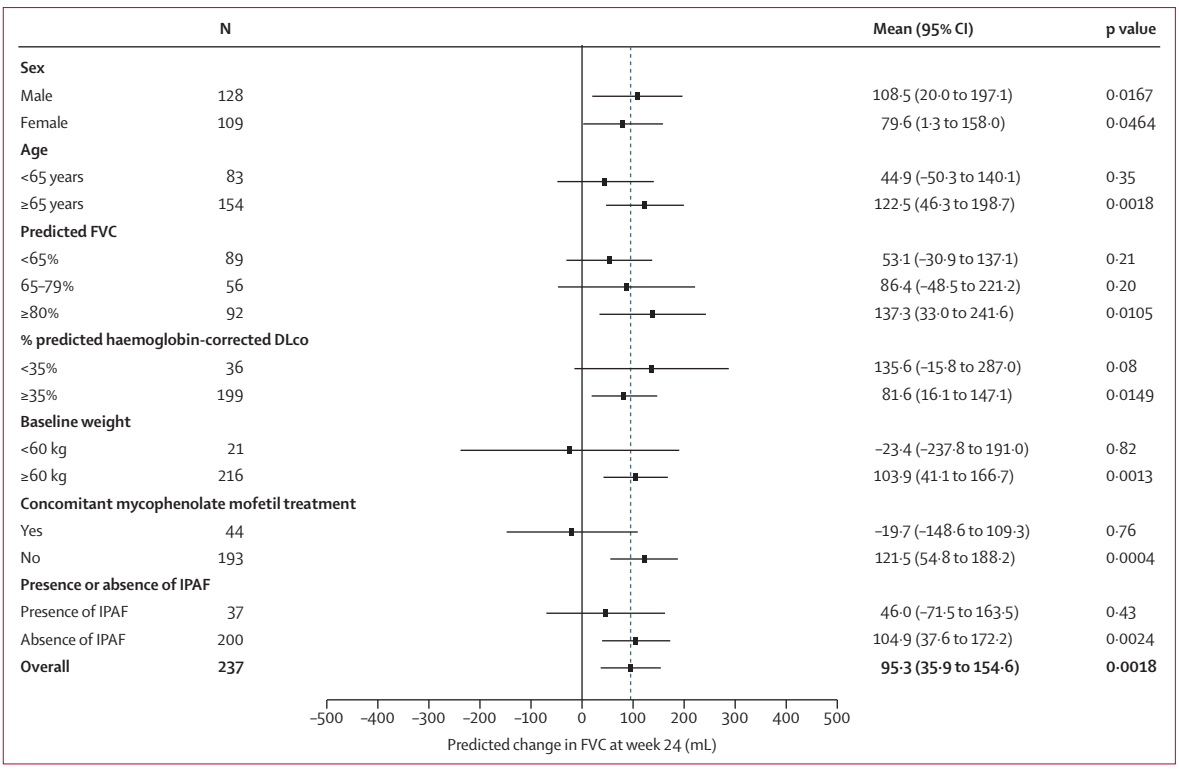

Figure 3: **Subgroup analysis of mean change in FVC from baseline at week 24 measured by site spirometry in all patients who had site spirometry at week 8 (n=237)**

FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. IPAF=interstitial pneumonia with autoimmune features.

treatment group), which were not deemed to be treatment-related. Treatment-emergent adverse events by System Organ Class are shown in the appendix (p 9).

Discussion

In this randomised, controlled trial of pirfenidone in patients with progressive fibrosing unclassifiable ILD, the planned statistical model could not be applied to the primary endpoint data. However, results for the key secondary endpoints support the conclusion that 24 weeks of treatment with pirfenidone slows disease progression when compared with placebo in patients with progressive fibrosing unclassifiable ILD. The safety and tolerability profile of pirfenidone was comparable with that in patients with IPF,[16] and no new safety signals were identified.

The analysis of the primary endpoint in this study was affected by unanticipated technical and analytical issues with home spirometry. In some patients with short observation periods, the application of linear regression to predict FVC change after 24 weeks of treatment generated extreme outliers that led to physiologically implausible values. Technical problems with the algorithm that determined recording of daily spirometry readings also contributed to these outliers, with spirometers recording implausibly low (<0·5 L) or high (>6 L) readings approximately 2·7% of the time. Many of the issues occurred because the spirometers were set up to record only one acceptable blow per day (intended to improve patient compliance and minimise the intrusiveness of taking readings), but many of the inbuilt quality control features, including measurement of intrablow differences of blows done on the same day, could only be activated if three blows were permitted per day. This resulted in undetected day-to-day variability and physiologically impossible values. Daily home spirometry has been previously studied in IPF,[17–19] and although the data collected can be variable,[19] the issues encountered during this study could not have been predicted. The technical issues associated with home spirometry meant that the planned statistical model could not be applied to the primary endpoint data, and it is now clear that further analyses, including an assessment of how to do clinical trials using home spirometry and the application of various analytical approaches to determine which is the most appropriate, are needed before this method can be used in future trials.

In this study, results favouring pirfenidone compared with placebo were observed across several secondary efficacy endpoints, suggesting that pirfenidone is effective in patients with progressive fibrosing unclassifiable ILD. When using site spirometry to monitor FVC, which is the accepted regulatory standard in IPF clinical trials,[20] predicted 24-week decline (estimated by linear regression)

in FVC was 95·3 mL lower in patients given pirfenidone compared with placebo. Although not directly comparable because of differences in handling of missing data, this result is similar to the treatment benefit observed on mean decline in FVC in a prespecified pooled analysis of the phase 3 trials of pirfenidone in IPF, in which an absolute treatment difference of 104 mL was observed for pirfenidone versus placebo after 24 weeks of treatment, increasing to 148 mL after 52 weeks of treatment.[21] Furthermore, in the current study, fewer patients treated with pirfenidone reported an absolute or relative decline in percent predicted FVC of more than 5% or an absolute decline in percent predicted FVC of more than 10% than did patients in the placebo group. No differences in the proportion of patients with more than 10% relative decline in percent predicted FVC were observed between groups. Mean change in FVC from baseline at week 24 measured using site spirometry was also assessed in an exploratory subgroup analysis, which found that a treatment benefit was generally observed with pirfenidone regardless of age, sex, lung function, and presence or absence of interstitial pneumonia with autoimmune features. Although the SENSCIS study of nintedanib in ILD associated with systemic sclerosis reported that the treatment effect of nintedanib on FVC change was affected by mycophenolate mofetil,[22] we were unable to draw any such conclusions about the possible influence of mycophenolate mofetil on the effect of pirfenidone in this study because of the small sample sizes. Similarly, the small number of patients included in the low bodyweight subgroup prevented any meaningful conclusions being drawn from this analysis.

Additional secondary and exploratory endpoints included DLco, 6MWD, and progression-free survival. Although the results of rank ANCOVA analysis for percent predicted DLco did not favour pirfenidone, the prespecified exploratory analysis of the proportion of patients with a more than 15% categorical decline in percent predicted DLco did show a treatment benefit. By contrast, rank ANCOVA analysis of the 6MWD results favoured pirfenidone, but the prespecified exploratory analysis of the proportion of patients with a more than 50 m categorical decline did not. Results for both definitions of progression-free survival used in this study did not show a treatment difference. Secondary outcomes also included patient-reported outcomes (UCSD-SOBQ score, Leicester Cough Questionnaire score, cough visual analogue scale, and SGRQ score) and, consistent with IPF studies, changes from baseline were similar between the pirfenidone and placebo groups.[8,9]

The safety outcomes from this study were consistent with the established safety profile of pirfenidone in patients with IPF, with the type and frequency of treatment-emergent adverse events identified in this study similar to those observed in phase 3 IPF trials.[16] The proportion of patients treated with pirfenidone who had serious treatment-related, treatment-emergent adverse events (1%) or severe treatment-related treatment-emergent adverse events (5%) was low, and no new safety signals were identified.

	Pirfenidone (n=127)	Placebo (n=124)
Any treatment-emergent adverse events	120 (94%)	101 (81%)
Any treatment-related treatment-emergent adverse events	90 (71%)	57 (46%)
Any serious treatment-emergent adverse events*	18 (14%)	20 (16%)
Any severe treatment-emergent adverse events	29 (23%)	28 (23%)
Any treatment-related, severe treatment-emergent adverse events	6 (5%)	2 (2%)
Treatment-emergent adverse events of special interest†	0	0
Treatment-emergent adverse events leading to death	1 (1%)	1 (1%)
Treatment-related, treatment-emergent adverse events leading to death	0	0
Treatment-emergent adverse events leading to treatment discontinuation	19 (15%)	5 (4%)
Treatment-related, treatment-emergent adverse events leading to treatment discontinuation	16 (13%)	1 (1%)
Treatment-related treatment-emergent adverse events known to be associated with pirfenidone		
Gastrointestinal disorder‡	60 (47%)	32 (26%)
Photosensitivity§	10 (8%)	2 (2%)
Rash¶	13 (10%)	9 (7%)
Dizziness	10 (8%)	4 (3%)
Weight decrease	10 (8%)	1 (1%)
Fatigue	16 (13%)	12 (10%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. MedDRA=Medical Dictionary for Regulatory Activities. ULN=upper limit of normal. *Only one treatment-emergent adverse event in each treatment group was considered to be treatment-related. †Cases of potential drug-induced liver injury that include ALT or AST elevations in combination with elevated bilirubin concentrations or clinical jaundice, defined by Hy's law (ALT or AST >3 × ULN + total bilirubin >2 × ULN). ‡MedDRA System Organ Class gastrointestinal disorders. §Includes MedDRA preferred terms photodermatosis, photosensitivity reaction, pruritus, pruritus allergic, and pruritus generalised. ¶Includes MedDRA preferred terms nodular rash, rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash follicular, exfoliative rash, solar dermatitis, solar urticarial, sunburn, erythema, and dry skin.

Table 4: **Treatment-emergent adverse events in the safety analysis set (n=251)**

The results of this study are important because at present no direct evidence is available to guide the treatment of patients with unclassifiable ILD, and no approved pharmacological treatments exist. In clinical practice, management is often based on the most probable diagnosis.[5,7] Several parallels in disease behaviour can be drawn between progressive fibrotic unclassifiable ILD and IPF[3] on the basis of similarities in disease progression and prognosis. Considering available data for both patient populations, patients with IPF given placebo in the ASCEND phase 3 trial of pirfenidone showed a linear slope of decline in FVC of 280 mL at week 52, whereas patients with unclassifiable ILD given placebo in our study had a mean decline of 113·0 mL at week 24 measured using site spirometry.[8] Although not directly comparable, because during ASCEND patients who died had their FVC imputed as 0 mL and therefore the decline was larger,[8] these data illustrate the progressive nature and decline in lung function shared by both patients with IPF and progressive fibrosing unclassifiable ILD. The results of this study indicate that the similarities in disease behaviour between IPF and

progressive fibrosing unclassifiable ILD might extend to treatment response, with pirfenidone showing efficacy in this subgroup of patients with unclassifiable ILD.

Our study had several limitations that should be considered when interpreting the results. In addition to the problems associated with home spirometry, patients with unclassifiable ILD represent a heterogeneous population, thus the treatment effect might vary on a case-by-case basis. Although most patients in this study had a diagnosis of unclassifiable ILD without any features suggestive of another form of ILD, we cannot exclude the possibility that some patients, who did not have a biopsy and were considered to have unclassifiable ILD in this study, might have had an underlying pathological pattern of usual interstitial pneumonia typical of IPF. However, it should be noted that even patients with an IPF diagnosis made with low confidence were excluded from this study. In this study, patients had to receive a diagnosis of unclassifiable ILD based on the consensus of a multidisciplinary board. Investigators received training on the inclusion and exclusion criteria of this study, which were developed on the basis of the available literature on unclassifiable ILD,[7] and they were provided with a number of case studies, which can be viewed online.[12] A further limitation associated with diagnosis is that high-resolution CT images were not collected, thus, although investigators had to confirm that patients had more than 10% fibrosis to be eligible for the study, this was not independently verified, and more detailed profiling of fibrotic and inflammatory changes was not done. Similarly, although investigators were asked to evaluate the presence or absence of interstitial pneumonia with autoimmune features using the published research criteria,[15] the individual components of the interstitial pneumonia with autoimmune features score were not recorded. The short treatment duration was another limitation, with patients only treated for 24 weeks; however, the difference in FVC between groups measured by hospital site spirometry was highly differentiated at 24 weeks and the study length limited the duration of time that patients could receive placebo.

This study identified several important methodological challenges associated with home spirometry, which ultimately prevented the application of the prespecified statistical model to the primary endpoint data. Further research is needed to address the challenges encountered with this outcome measure. However, the results from several of the key secondary and exploratory outcomes, including lung function and exercise capacity, suggest that pirfenidone could be an effective treatment for patients with progressive fibrotic unclassifiable ILD over 24 weeks, with an acceptable safety and tolerability profile, and these results warrant further investigation.

Contributors

All authors were involved in conceptualisation of the study and data interpretation, and all contributed to writing of the manuscript and read and approved the final draft.

Declaration of interests

TMM has received grants from GlaxoSmithKline, UCB, and AstraZeneca via his institution; has received consultancy or speakers fees from Apellis, AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Galapagos, GlaxoSmithKline, Indalo, Novartis, Pliant, ProMetic, Respivant, F Hoffmann-La Roche, Samumed, and UCB; and owns stock options in Apellis. TJC has received unrestricted educational grants, travel assistance, and speaker fees, and has served on advisory boards for Boehringer Ingelheim; has received unrestricted educational grants and speaker fees, and has served on advisory boards for F Hoffmann-La Roche; has received unrestricted educational grants from Actelion, Bayer, Galapagos, and Sanofi; and has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, and Promedior. AF served as a consultant and clinical trial steering committee member for Boehringer Ingelheim and F Hoffmann-La Roche, and as a consultant for Bristol-Myers Squibb and Pfizer; AF is now a full-time employee of Bristol-Myers Squibb. MK, or his institution, has received unrestricted educational grants, speaker fees, research grants, and advisory board fees from Boehringer Ingelheim and F Hoffmann-La Roche; and received advisory board fees from Galapagos. DJL is a steering committee member for this study; and has received consultancy or advisory board fees from Boehringer Ingelheim, Fibrogen, Galapagos, Genentech/Roche, Global Blood Therapeutics, Immuneworks, Philips Respironics, and Veracyte. DJL's previous institution (Columbia University) has received support and fees for clinical trials or consulting services from Boehringer Ingelheim, Fibrogen, Global Blood Therapeutics, and the Pulmonary Fibrosis Foundation. DJL is now a full-time employee of Regeneron Pharmaceuticals. MM-M has received grants from AstraZeneca, Boehringer Ingelheim, BRN, Chiesi, GlaxoSmithKline, InterMune (a wholly owned subsidiary of F Hoffmann-La Roche since 2014), and F Hoffmann-La Roche; and personal fees from Esteve-Teijin Healthcare outside of the submitted work. JA and K-UK are employees and shareholders of F Hoffmann-La Roche. KS and FG are employees of F Hoffmann-La Roche. VC reports personal fees and consultancy fees, lecture fees, and travel expenses from Actelion; grants, personal fees, and consultancy fees, lecture fees, and travel expenses from Boehringer Ingelheim, personal fees from Bayer/MSD, Gilead, Novartis, Promedior, Celgene, Galapagos, and Galecto; grants, personal fees, and non-financial support from Roche; and grants from Sanofi, outside of the submitted work.

Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). 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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