

Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial



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Summary

Background Pirfenidone has been shown to slow disease progression in patients with idiopathic pulmonary fibrosis (IPF). However, there are few treatment options for progressive fibrotic interstitial lung diseases (ILDs) other than IPF. In view of the pathomechanistic and clinical similarities between IPF and other progressive fibrotic ILDs, we aimed to assess the efficacy and safety of pirfenidone in patients with four non-IPF progressive fibrotic ILDs.

Methods We did a multicentre, double-blind, randomised, placebo-controlled, parallel phase 2b trial (RELIEF) in 17 centres with expertise in ILD in Germany. Eligible participants were patients aged 18–80 years with progressive fibrotic ILD due to four diagnoses: collagen or vascular diseases (ie, connective tissue disease-associated ILDs), fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis. Other eligibility criteria included a forced vital capacity (FVC) of 40–90% predicted, a diffusing capacity of the lung for carbon monoxide (DLCO) of 10–90% predicted, and an annual decline of FVC of at least 5% predicted despite conventional therapy, based on at least three measurements within 6–24 months before enrolment. Patients who had received any previous antifibrotic therapy were excluded. We randomly assigned patients (1:1) to either oral pirfenidone (267 mg three times per day in week 1, 534 mg three times per day in week 2, and 801 mg three times per day thereafter) or matched placebo, added to their ongoing medication. Randomisation was done centrally using permuted block randomisation with varying block sizes stratified by the four diagnostic groups. Patients, investigators, statisticians, monitors, and the study coordinator were masked to treatment assignment until database closure. The placebo-controlled study period was 48 weeks (including up-titration). The primary endpoint was absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48 in the intention-to-treat population, with imputation of missing data by the smallest sum of squared differences (SSD) and attribution of deceased patients to the lowest rank in a rank ANCOVA model. Additionally, we did linear mixed-model repeated measures slope analyses of FVC % predicted longitudinal data over the course of the study as a prespecified sensitivity analysis and post-hoc sensitivity analyses of the primary endpoint in the intention-to-treat population using imputation methods of last observation carried forward [LOCF] and a regression-based multiple imputation procedure. Safety was assessed in all patients who received at least one dose of study medication. This trial is registered with EudraCT 2014-000861-32; DRKS00009822 and is no longer recruiting.

Findings Between April 5, 2016, and Oct 4, 2018, we randomly assigned 127 patients to treatment: 64 to pirfenidone, 63 to placebo. After 127 patients had been randomised, the study was prematurely terminated on the basis of an interim analysis for futility triggered by slow recruitment. After 48 weeks and in the overall population of 127 patients, rank ANCOVA with diagnostic group included as a factor showed a significantly lower decline in FVC % predicted in the pirfenidone group compared with placebo ($p=0.043$); the result was similar when the model was stratified by diagnostic group ($p=0.042$). A significant treatment effect was also observed when applying the LOCF and multiple imputation methods to analyses of the primary endpoint. The median difference (Hodges-Lehmann estimate) between pirfenidone and placebo groups for the primary endpoint was 1.69 FVC % predicted (95% CI -0.65 to 4.03). In the linear mixed-model repeated measures slope analysis of FVC % predicted, the estimated difference between treatment and placebo groups from baseline to week 48 was 3.53 FVC % predicted (95% CI 0.21 to 6.86) with imputation of deaths as prespecified, or 2.79 FVC % predicted (95% CI 0.03 to 5.54) without imputation. One death (non-respiratory) occurred in the pirfenidone group (2%) and five deaths (three of which were respiratory) occurred in the placebo group (8%). The most frequent serious adverse events in both groups were infections and infestations (five [8%] in the pirfenidone group, ten [16%] in the placebo group); general disorders including disease worsening (two [3%] in the pirfenidone group, seven [11%] in the placebo group) and cardiac disorders (one [2%] in the pirfenidone group, 5 [8%] in the placebo group). Adverse events (grade 3–4) of nausea (two patients on pirfenidone,

Lancet Respir Med 2021

Published Online

March 29, 2021

[https://doi.org/10.1016/S2213-2600\(20\)30532-4](https://doi.org/10.1016/S2213-2600(20)30532-4)

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See Online for appendix 1

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See Online for appendix 2

two on placebo), dyspnoea (one patient on pirfenidone, one on placebo), and diarrhoea (one patient on pirfenidone) were also observed.

Interpretation In view of the premature study termination, results should be interpreted with care. Nevertheless, our data suggest that in patients with fibrotic ILDs other than IPF who deteriorate despite conventional therapy, adding pirfenidone to existing treatment might attenuate disease progression as measured by decline in FVC.

Funding German Center for Lung Research, Roche Pharma AG.

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Introduction

There is a spectrum of interstitial lung diseases (ILDs), almost all of which carry a risk of developing a progressive fibrotic ILD phenotype.¹ Of note, idiopathic pulmonary fibrosis (IPF), the most aggressive fibrotic ILD, and other forms of progressive fibrotic ILD share several clinical and pathomechanistic similarities, including excess morbidity and mortality.² From the published literature and our clinical experience, the non-IPF progressive fibrotic ILD phenotype is most prominently represented

by four entities: (1) lung fibrosis in association with collagen or vascular diseases (ie, connective tissue disease-associated ILDs), (2) fibrotic non-specific interstitial pneumonia, (3) chronic hypersensitivity pneumonitis, and (4) asbestos-induced lung fibrosis.³

The current standard of care for non-IPF ILDs largely consists of systemic steroids or immunosuppressive drugs, but this is based on weak evidence.¹ Two small molecule drugs, pirfenidone and nintedanib, inhibit pro-fibrotic and pro-inflammatory pathways involved in

Research in context

Evidence before this study

We searched PubMed from database inception to September 30, 2020, for English-language publications with the terms “PF-ILD” OR “progressive fibrosing interstitial lung disease” OR “progressive fibrosing ILD” OR (“progressive fibrosing” AND [“interstitial lung disease” OR “ILD”]), which yielded 64 articles. After excluding publications that were not in English or not related to progressive fibrosing interstitial lung disease (ILD), 54 articles remained. To focus on the treatment of progressive fibrotic ILD, we then excluded case studies and articles on the basic science, prevalence or incidence, diagnosis, disease classification, natural history, or prognosis, which left 35 articles. 29 of these were reviews, perspectives, or educational articles and were excluded. Of the remaining six articles, three reported study protocols and one was a sub-group analysis of the main study. Thus, our search identified two randomised placebo-controlled trials, one using nintedanib in progressive fibrotic ILD (INBUILD) and one using pirfenidone in unclassifiable ILD. While INBUILD was clearly positive for the primary endpoint of annual decline in forced vital capacity (FVC), the primary endpoint of mean predicted change in FVC from baseline over 24 weeks measured by daily home spirometry in the unclassifiable ILD trial was not positive for technical reasons leading to inconsistent measurements, but showed significantly positive results for key secondary endpoints including decline in FVC at week 24 with centre-based spirometry. In addition, a search of the authors’ own references of included studies identified a trial of nintedanib showing benefit in patients with systemic sclerosis and ILD associated with systemic sclerosis involving at least 10% of the lung parenchyma on high-resolution CT (SENSCIS trial). A search of clinicaltrials.gov did not reveal new ongoing trials in

this area. Except for our study, we did not find any randomised controlled trials investigating pirfenidone in patients with progressive fibrotic ILD.

Added value of this study

In our trial, we investigated the efficacy and safety of pirfenidone versus placebo in addition to standard of care in patients with progressive fibrotic ILD due to idiopathic non-specific interstitial pneumonia, connective tissue disease-associated ILD, chronic hypersensitivity pneumonitis, and asbestos-induced lung fibrosis, a substantial and broad subset of all progressive fibrotic ILDs. The progressive nature of the underlying disease was evident from a clinically relevant decline in FVC of at least 5% predicted per year, despite standard therapy. As a result of an interim analysis triggered by unanticipated slow recruitment, our study was terminated early for futility after enrolment of 127 patients. Despite this limitation, we observed encouraging signals in primary and secondary endpoints: pirfenidone treatment seemed to be associated with benefits in lung function compared with placebo after 48 weeks of treatment. In addition, mortality and other serious adverse events, and pulmonary infections leading to adverse events, were numerically lower in the pirfenidone group.

Implications of all the available evidence

In the context of other clinical trials investigating pirfenidone in unclassifiable ILD and nintedanib in progressive fibrotic ILD (INBUILD and SENSCIS), our study adds further support for the concept that patients with progressive, non-IPF fibrotic ILD seem to be similarly responsive to antifibrotic therapy as those with IPF, and we suggest that antifibrotic therapy represents a new standard of care in treatment of progressive fibrotic ILDs.

the fibrotic disease process.² Nintedanib has also been approved in the EU for the treatment of other progressive fibrotic ILDs,^{4,5} whereas the safety and effectiveness of pirfenidone for the treatment of non-IPF progressive fibrotic ILDs remain unclear. In patients with IPF, pirfenidone at a dose of 801 mg three times per day reduced the rate of decline in forced vital capacity (FVC)^{1,2,6,7} and improved survival.^{6,7} Pirfenidone has also been shown to reduce disease progression in progressive unclassifiable fibrosing ILDs.⁸

In view of the pathomechanistic and clinical similarities to IPF, we did the RELIEF trial to investigate the efficacy and safety of pirfenidone in patients with the four ILD entities mentioned earlier with documented functional deterioration despite conventional therapy, as a representative subset of progressive fibrotic ILDs other than IPF. As an objective criterion of disease progression despite conventional therapy we included only patients who showed an annualised decline of FVC of at least 5%, as documented by at least three spirometry measurements within 6–24 months before study inclusion.

Methods

Study design and participants

We did a multicentre, double-blind, randomised, placebo-controlled, parallel phase 2b trial (RELIEF) in 17 centres with expertise in ILD throughout Germany under the auspices of the German Center for Lung Research (DZL) to investigate efficacy and safety of pirfenidone in progressive fibrotic ILD. The study was approved by the central ethics committee of the University of Munich (Munich, Germany; registration number 473-15 fed) and by institutional review boards at all participating sites. The study protocol was published in detail previously⁹ (appendix 2 pp 2–142).

Eligible patients were men and women aged 18 to 80 years who had a diagnosis of CTD-ILD, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis, with an FVC of between 40% and 90% predicted and a haemoglobin-adjusted diffusing capacity of the lung for carbon monoxide (DLCO) of 25–75% predicted at baseline. DLCO criteria were extended to 10–90% as part of a protocol amendment to increase the enrolment rate on July 7, 2016. Confirmation of diagnosis included results of previous surgical lung biopsies or high-resolution CT scans done within 6 months before randomisation if available. There was no central review of surgical lung biopsies or CT scans. Full diagnostic criteria are in the published study protocol⁹ (appendix 2 pp 25–26). To prove disease progression despite conventional therapy, an annual FVC decline of at least 5% predicted, based on at least three FVC measurements within 6–24 months before enrolment, was mandatory. We excluded patients who had received any antifibrotic therapy previously. Detailed entry criteria

are in the study protocol (appendix 2 pp 98–102). All patients provided written informed consent.

Randomisation and masking

We randomly assigned patients (1:1) to either oral pirfenidone or matched placebo. Randomisation was done centrally with randomly permuted blocks of size two, four, or six by the Center for Clinical Trials of the University of Marburg (Marburg, Germany) and was stratified by diagnostic group (appendix 2, p 102). To ensure allocation concealment, randomisation lists were generated by a data manager who was not involved in the trial beyond that role. The randomisation result for each included patient was requested via telefax authorisation form and then reported back to the centre in the form of a Med-ID. Patients, investigators, coordinating clinical investigators, statisticians, monitors, and the study coordinator were masked to treatment assignment. Maintenance of masking at investigational sites was continually ensured at each monitoring visit from site initiation until close-out; masking of treatment allocation was maintained during interim analysis until database closure.

Procedures

After randomisation, patients received pirfenidone or placebo in addition to their ongoing medication, starting with 267 mg three times per day for the first week, 534 mg three times per day for the second week, and 801 mg three times per day thereafter. The placebo-controlled study period was 48 weeks (including up-titration), followed by an open label extension during which pirfenidone was provided to all patients until the last patient completed the study. Study site-based spirometry was done at baseline and at weeks 12, 24, 36, and 48. Chest x-rays or high-resolution CT were done in case of clinical deterioration and suspected exacerbation. The full schedule of assessments done at the screening visit and at each site visit during the study is available in the protocol (appendix 2, p 38).

Outcomes

The primary endpoint was the absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48, assessed centrally. Secondary endpoints were progression-free survival, categorical assessment of relative changes from baseline to week 48 in predicted FVC of less than 5%, 5% to less than 10%, and at least 10%, DLCO, exercise capacity (6-min walk distance [6MWD]), quality of life (St George's Respiratory Questionnaire [SGRQ]), time to clinical deterioration, and safety (frequencies of adverse events and serious adverse events). Change from baseline to week 48 in the worst oxygen saturation by pulse oximetry (SpO₂) measurement observed during the 6MWT and EQ-5D questionnaire results were foreseen as secondary outcomes in the study protocol; however, sample sizes for these outcomes were

small ($n < 60$), and there was heavy overdispersion in the case of changes in SpO_2 and a highly skewed distribution in the case of EQ5D responses, therefore these outcomes were not included in this report.

Progression-free survival was defined as alive and no decrease in the absolute FVC % predicted compared with the baseline value of more than 10% and no decrease in the absolute percentage of predicted DLCO versus the baseline value of more than 15%. For the purpose of this study, clinical deterioration was defined by the following three criteria: clinical worsening of dyspnoea within 4 weeks; and new or worsening radiographic abnormalities on chest x-ray or high-resolution CT; and objective worsening of pulmonary function tests or gas exchange, which was defined by at least one of the following criteria: initiation of long-term oxygen therapy or increase of oxygen supplementation of existing long-term oxygen therapy by at least 1 L/min to maintain resting oxygen saturation of at least 90%; a drop in FVC by more than 10% compared with the previous measurement; a drop in DLCO by more than 15% compared with the previous measurement; or a drop in 6MWD by 20% compared with the previous measurement.

Similar to previous studies,^{5,7,8} we assessed the absolute change in FVC (mL) from baseline to week 48 in a post-hoc analysis. Additionally, two other lung function parameters, total lung capacity (TLC) and FEV_{12} , were assessed in post-hoc analyses to underpin FVC changes in this heterogeneous group of patients with ILDs with potential for obstructive ventilatory impairment such as chronic hypersensitivity pneumonitis.

Statistical analysis

For the primary efficacy analysis, a group sequential design with one interim analysis according to O'Brien and Fleming¹⁰ was taken into account for the calculation of sample size (appendix 2, pp 138–40). Given a two-sided significance level of 5%, a power of 80%, and a drop-out rate of 5%, 187 patients per group (ie, 374 patients in total) would have been required to detect an effect size of 0.3 between the treatment and placebo groups. However, low recruitment (appendix 1, p 12) prompted an early interim analysis on April 11, 2018, requested and done by the data monitoring committee. As a result of this analysis, the committee recommended stopping the study because of futility (appendix 2, pp 159–65).

In general, all efficacy endpoints were analysed in the intention-to-treat population, but a prespecified per-protocol analysis of the primary endpoint was additionally provided for the sensitivity analysis. Safety analyses included all randomly assigned patients who received at least one dose of study medication.

As the primary efficacy endpoint was assumed to be not normally distributed,⁹ we fitted a rank ANCOVA model with classification effect for the treatment and diagnostic categories (appendix 1, p 2) and baseline FVC values as covariates. The applied rank ANCOVA model

also was stratified (fixed effect) by diagnostic categories and the treatment effect was tested in a stratified mean score test using Cochran-Mantel-Haenszel statistics on the model residuals as scores. To prevent inflation of type I error rates from multiple comparisons when testing the treatment effect in different groups with regard to diagnosis, a hierarchical testing procedure (appendix 2, p 137) was done. Accordingly, the treatment effect was repeatedly tested in a fixed sequence after removal of each of the specific diagnostic groups (ordered by group size) until the p value exceeded the 5% significance level. Furthermore, assuming a similar treatment effect in all clinical diagnosis groups (diagnostic categories in the appendix 2, pp 138–39) on the primary endpoint, the Mann-Whitney *U* test for independent samples was used to test for a difference between treatment and placebo groups. Point estimates for the median difference between groups with 95% CI were calculated using the Hodges-Lehmann method.

For analyses of the primary endpoint, as prespecified, missing data were imputed sequentially over visits by averaging the non-missing data of the three patients with the smallest sum of squared differences (SSD) at the previous visit (similar to the statistical analysis applied in the CAPACITY and ASCEND trials of pirfenidone in patients with IPF;^{6,7} appendix 2, pp 140–41). For the rank ANCOVA-based analyses and the Mann-Whitney *U* test, patients with missing values due to death were assigned the worst rank according to the time from randomisation until death, with the shortest time until death corresponding to the worst rank. This decision was based on the assumption that patients who have died would, on average, have a greater FVC decline and therefore missing values of deceased patients cannot be considered as missing at random. By contrast, although the routine causes of missing data in this trial (eg, withdrawals and exclusions) might be regarded as not missing at random, in this case, the decision by the central ethics committee to prematurely terminate the trial led to missing data that affected all patients without distinction and can therefore be considered as missing at random and not a source of bias. Because of the differences in missing data mechanisms introduced by the premature termination of the trial, as post-hoc sensitivity analyses for the rank ANCOVA-based analysis of the primary endpoint, we also did a last observation carried forward analysis (LOCF) and a regression-based multiple imputation procedure to assess the robustness of our estimates against different imputation models and the exclusion of deceased patients.

A linear mixed-model repeated measures slope analysis for change from baseline in FVC % predicted was done as an additional prespecified sensitivity analysis. For this analysis, missing data generally were not imputed. However, in the case of patients who died, the first missing data value after time of death was replaced with an FVC % predicted of 30 (approximately

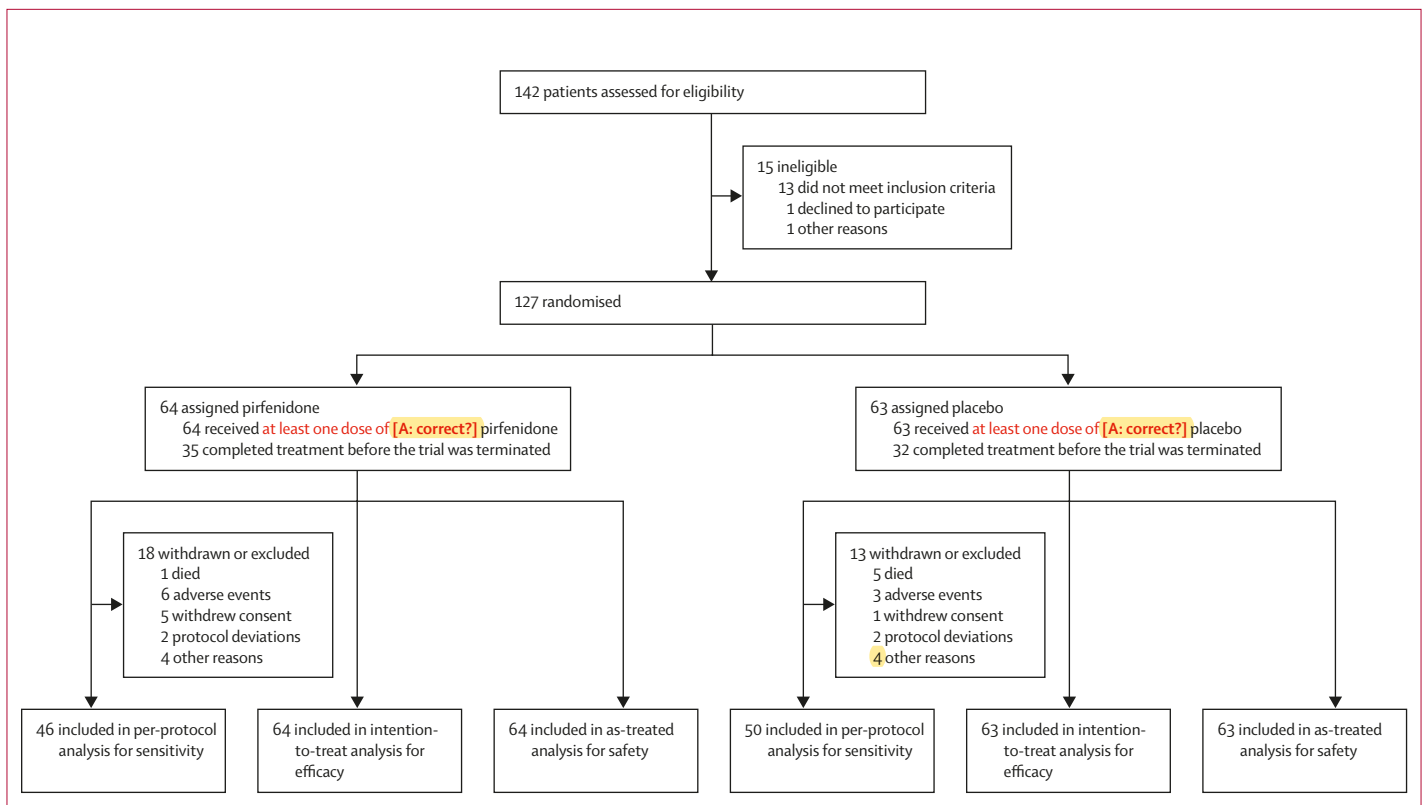


Figure 1: Trial profile

In 29 (26%) of all included patients, outcome data on the primary endpoint were still missing when being asked by the central ethics committee to actively withdraw patients from further study participation; as a result, data for 60 patients in total (47%) needed to be imputed [A: in the 'withdrawn or excluded' boxes, totals do not add up; did patients qualify for more than one reason?].

representing the 1% quantile of values observed in our cohort, which was FVC 31.1% predicted). Subsequent values were not imputed. The mixed model included fixed effects for treatment, diagnostic group, and assessment week (with interaction term between treatment and assessment week), covariates for baseline FVC % predicted, and a random intercept term of patient grouped by a factor for trial site. For further checking of the robustness of the derived model estimates, this model was also fitted to the (unimputed) raw data as a post-hoc analysis. To facilitate the validation of FVC measurements and the calculation of FVC slopes, a web application provided by the DZL was made available to the study investigators.

For the prespecified secondary endpoints of DLCO, 6MWD, and quality of life (SGRQ), as well as FVC, TLC, and FEV₁ in post-hoc analyses, the Mann-Whitney *U* test for independent samples was used to test for a difference between the treatment and placebo groups. As before, point estimates and 95% CI of the treatment effect were calculated using the Hodges-Lehmann method. To compare event time distributions for progression-free survival and drug exposure times, we used the Kaplan-Meier method and log-rank tests. Patients who prematurely withdrew from the study were censored on the day of their last clinic visit before

discontinuing the study drug. Categorical changes in FVC % predicted (<5%, 5% to <10%, and ≥10%) according to treatment and placebo groups were assessed descriptively. Time to clinical deterioration and adverse events were also summarised descriptively. For secondary and exploratory endpoints, there was no imputation for missing data. Statistical results reported for secondary and exploratory endpoints were not corrected for multiple testing.

In a post-hoc analysis, the absolute change in FVC % predicted from baseline to the end of the open label extension phase was assessed. Additionally, we included sex and oxygen supply at baseline as covariates in the rank ANCOVA model with the hierarchical testing procedure for the primary endpoint as a post-hoc sensitivity analysis.

All analyses were done with SAS (version 9.4 M3), and ggplot2¹¹ for the R environment¹² was used for creating some of the figures. An independent data monitoring committee oversaw the study. This study is registered with EudraCT 2014-000861-32; DRKS00009822.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Pirfenidone (n=64)	Placebo (n=63)
Age, years	63.2 (10.6)	63.5 (9.1)
Sex		
Men	43 (67%)	32 (51%)
Women	21 (33%)	31 (49%)
Supplemental O ₂ at rest	14 (22%)	20 (32%)
Flow rate at rest, L/min	2.2 (0.9)*	2.3 (0.8)†
FVC, % predicted	62.6 (14.5)	62.2 (13.5)
FEV ₁ , % predicted	68.1 (15.4)	64.4 (14.3)
DLCO, % predicted	38.1 (14.1)	37.7 (14.2)
FEV ₁ /FVC ratio	86.7 (6.9)	83.8 (7.7)
6MWD, m	357.7 (99.2)	345.2 (110.0)
Any steroid or immunosuppressant therapy	47 (73%)	56 (89%)
Steroid monotherapy	17 (27%)	31 (49%)
Combination therapy with steroids, all	23 (36%)	22 (35%)
Azathioprine	11 (17%)	11 (18%)
Mycophenolate	7 (11%)	6 (10%)

Data are mean (SD) or n (%). DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. 6MWD=6-min walk distance. *n=14. †n=20.

Table 1: Baseline demographic characteristics in the safety analysis population

Results

Between April 5, 2016, and Oct 4, 2018, we randomly assigned 127 patients to treatment: 64 to pirfenidone, 63 to placebo (figure 1). As a result of the interim analysis on April 11, 2018, prompted by slow recruitment (appendix 1, p 12), the data monitoring committee recommended stopping the study because of futility (appendix 2, pp 158–65) after 34% of the intended total sample size had been enrolled. After discussion with the central ethics committee, all patients had to stop further treatment and the last patient visit was on Oct 04, 2018. 29 (23%) of all included patients were asked by the ethics committee to be actively withdrawn from further study participation; as a result, data for 60 patients (47%) needed to be imputed.

The most frequent diagnosis of ILD was chronic hypersensitivity pneumonitis (57 patients [45%]), followed by CTD-ILD (37 patients [29%]), fibrotic non-specific interstitial pneumonia (27 patients [21%]), and asbestos-induced lung fibrosis (six patients [5%]). Within the CTD-ILD group, 17 patients (46%) were diagnosed with rheumatoid arthritis, eight (22%) with systemic sclerosis, five (14%) with Sjögren's syndrome, or polymyositis or dermatomyositis, three (8%) with mixed connective tissue disease, and four (11%) with an overlap syndrome not strictly attributable to just one of the other categories. Surgical lung biopsies confirming diagnosis were available for 30 patients (47%) in the pirfenidone group and 33 patients (52%) in the placebo group. The mean dose intensity in the pirfenidone and placebo groups was 92% and 97%, respectively, with mean doses of 2130.7 mg

(SD 382.7) pirfenidone and 2228.8 mg (300.9) placebo, and similar exposure times between the groups (appendix 1, p 13). Adherence rates (ie, the proportion of patients with a dose intensity of 80% or more) was about 53 (85%) of 62 in the pirfenidone group and 59 (95%) of 62 in the placebo group (three patients whose intake data were still missing at the timepoint of database closure have not been taken into account; appendix 1, p 13). Overall, the included patients in the treatment and placebo groups were similar in terms of demographic characteristics, lung function, and 6MWD (table 1). Additionally, the frequency and choice of steroid or immunosuppressant treatment did not differ between the groups (table 1; appendix 1, p 11).

In the rank ANCOVA analysis of the primary endpoint with diagnostic group included as a factor, treatment with pirfenidone resulted in a significantly lower decline from baseline to week 48 in FVC % predicted than placebo ($p=0.043$). Hierarchical testing proceeded after the exclusion of asbestos-induced lung fibrosis ($p=0.034$), but was stopped after excluding fibrotic non-specific interstitial pneumonia. The fixed-effects model stratified by diagnostic group showed a similar pattern ($p=0.042$ in the overall population, $p=0.041$ when asbestos-induced lung fibrosis was excluded, and was stopped after exclusion of fibrotic non-specific interstitial pneumonia). Assuming a similar treatment effect in all diagnostic groups, the Mann-Whitney U test for independent samples also indicated a difference between treatment and placebo groups ($p=0.049$; figure 2). The Hodges-Lehmann estimate for the median difference between groups for the primary endpoint was 1.69 FVC % predicted (95% CI -0.65 to 4.03). Analysis of data within the individual subgroups was not done as meaningful signals could not be calculated because of the small sample size.

In the analyses of secondary endpoints, no significant difference was found between the treatment and placebo groups with regard to progression-free survival (appendix 1, p 18). A categorical analysis of relative change from baseline to week 48 in FVC % predicted revealed a higher proportion of patients treated with pirfenidone (25 [71%]) than with placebo (15 [47%]) in the group of patients with less than 5% relative decline of FVC per year, whereas placebo patients were more frequent in the group of patients experiencing deterioration (ie, FVC decline $\geq 10\%$ per year; 13 placebo patients [40%] vs seven pirfenidone patients [20%]; appendix 1, p 19). There was a significant difference between groups for DLCO (without imputation of missing values), suggestive of a treatment effect of pirfenidone (table 2, figure 3). Similarly, the loss in 6MWD appeared to be less pronounced in the pirfenidone group versus the placebo group (table 2, figure 3), although this difference was not significant. For quality of life, assessed using the SGRQ, no between-group differences were noted (appendix 1, p 6).

The condition of clinical deterioration, as defined in this study, was met by two patients in the placebo

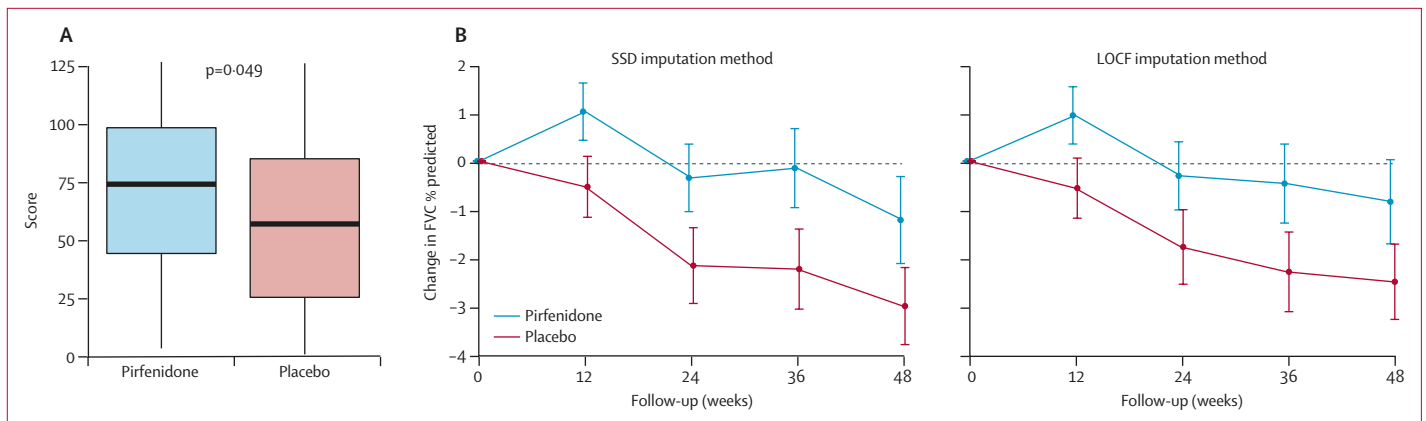


Figure 2: Absolute change in percentage of predicted FVC and time course for mean change in percentage of predicted FVC from baseline to week 48

(A) Distribution of Wilcoxon scores (from Mann-Whitney U test) for the absolute change in percentage of predicted FVC (FVC % predicted) from baseline to week 48 in the intention-to-treat population (n=127) for the pirfenidone and placebo groups (using the prespecified SSD imputation method for missing data, with deaths ranked worst). (B) Mean changes from baseline in FVC % predicted (SE) over the 48-week trial period in the pirfenidone and placebo groups after imputation of missing values (including those of deceased patients) according to the prespecified SSD method or, alternatively, the post-hoc LOCF imputation method. FVC=forced vital capacity. LOCF=last observation carried forward. SSD=sum of squared differences.

	Baseline		Change from baseline to week 48: within groups				Change from baseline to week 48: pirfenidone vs placebo	p value		
	n	Pirfenidone	n	Placebo	n	Pirfenidone			n	Placebo
FVC, mL	64	2332.5 (798.9)	63	2123.0 (715.7)	35	-36.6 (281.5)	32	-114.4 (225.3)	80.0 (-40.0 to 210.0)	0.21
DLCO, mmol/kPa per min	64	3.4 (1.4)	63	3.2 (1.2)	32	-0.1 (1.0)	26	-0.4 (0.6)	0.4 (0.1 to 0.7)	0.023
6MWD, m	64	357.7 (99.2)	63	345.2 (110.0)	33	-2.7 (74.2)	30	-34.1 (91.0)	28.0 (-15.0 to 75.0)	0.15
TLC, L	64	4.1 (1.2)	63	4.0 (1.0)	35	-0.1 (0.5)	32	-0.3 (0.4)	0.2 (0.0 to 0.4)	0.089
FEV ₁ , mL	64	2004.2 (636.2)	63	1761.7 (552.2)	35	-76.9 (259.3)	32	-103.1 (182.1)	50.0 (-50.0 to 140.0)	0.27

All analyses were done without imputation of missing values. Data are means (SD) at baseline, mean absolute changes (SD) from baseline to week 48, Hodges-Lehmann estimates for median differences (asymptotic 95% CIs) between pirfenidone and placebo, and two-sided p values from Mann-Whitney U tests. Note that FVC, TLC, and FEV₁ were assessed in post-hoc analyses. DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. TLC=total lung capacity. 6MWD=6-min walk distance.

Table 2: Absolute changes in lung function and exercise capacity from baseline to week 48

group (after 84 days and 169 days, respectively) and two patients in the pirfenidone group (after 176 days and 182 days, respectively). Consequently, rescue treatment with pulsed steroids was initiated in these four patients.

There were five deaths in the placebo group (8%) and one death in the pirfenidone group (2%). Of the five deaths in the placebo group, three were judged by the principal investigators to be respiratory driven. The cause of death of the patient in the pirfenidone group was found to be non-respiratory. The number of adverse events were equally distributed between the pirfenidone and placebo groups. Gastrointestinal side-effects (ie, nausea, vomiting, dyspepsia, decreased appetite, and weight loss) were slightly more frequent with pirfenidone, whereas dyspnoea and respiratory tract infections occurred slightly less frequently in the pirfenidone group (appendix 1, p 10).

There were numerically more serious adverse events in the placebo group than in the pirfenidone group (table 3), including infections and infestations, disease worsening, and cardiac disorders (listed according to the Medical Dictionary for Regulatory Activities, version 22.1; for a

full listing of serious adverse events according to preferred terms, see appendix p 174–175). Incidence of adverse events with and without underlying immunosuppressive therapy did not raise safety concerns (appendix 1, pp 8–9, 11). No new or unexpected adverse events were observed.

Missing data had been imputed by the SSD method for the prespecified primary outcome and deceased patients were assigned the worst rank (as outlined in the Methods), but in view of the changes in types and proportions of missing data, we undertook several post-hoc sensitivity analyses in the ITT population to further assess the robustness of the data. If, alternatively to SSD, other imputation methods were applied (ie, LOCF or multiple imputation), a similar, significant reduction in the FVC decline was noted applying the rank ANCOVA analysis (with deaths ranked worst); this was seen with diagnostic group included in the model as a classification effect (p=0.042 for LOCF; p=0.041 for multiple imputation) and with model stratification by diagnostic group (p=0.032 for LOCF; p=0.018 for

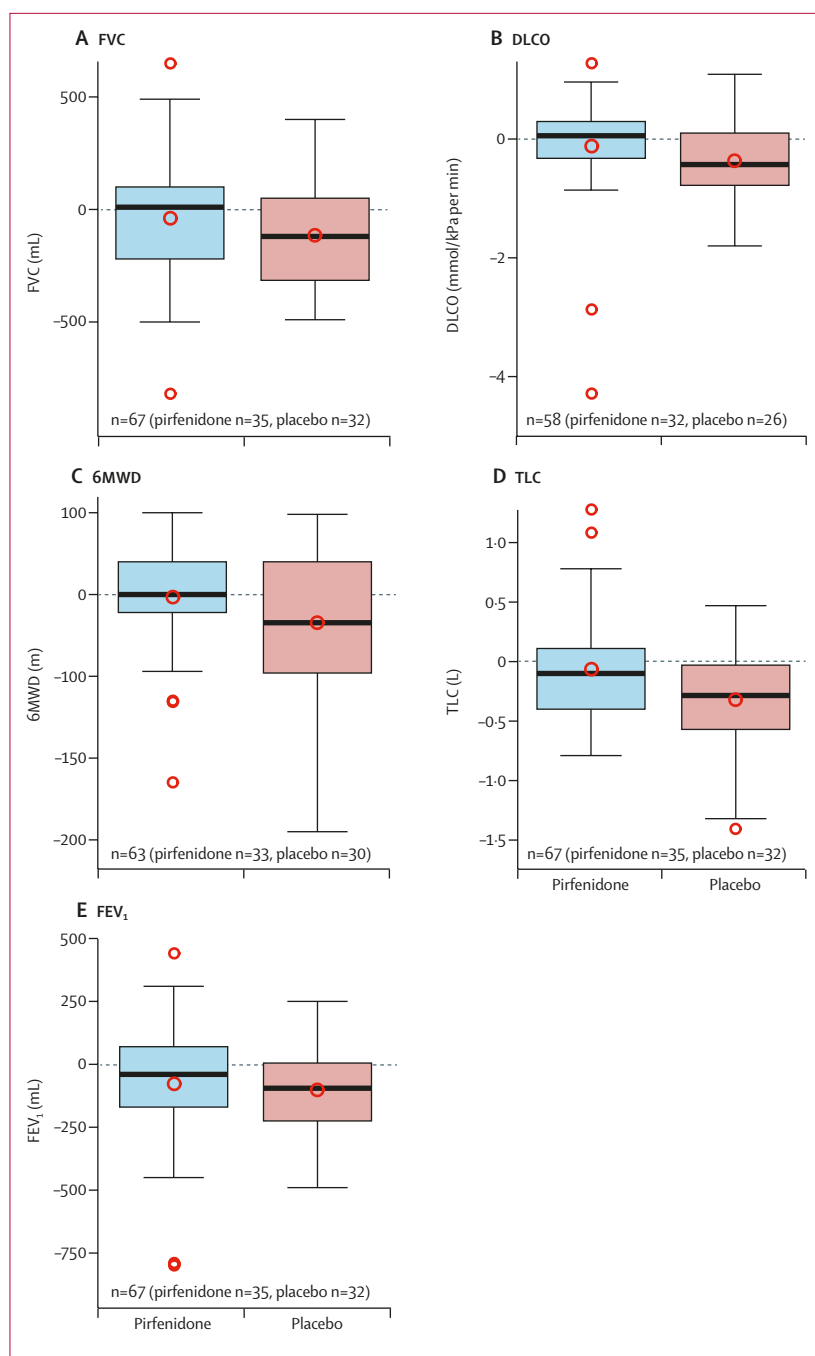


Figure 3: Absolute changes in lung function and exercise capacity from baseline to week 48

All analyses were done without imputation of missing values. Boxes show the IQR, median (midline), and mean (point marker). Whiskers show the spread of values beyond the box limits within a distance of $1.5 \times$ IQR. Green circles inside the box-plots indicate the respective mean values. Red circles outside the box-plots indicate outliers. p values are from two-sided Mann-Whitney U tests (table 2). (A) FVC=forced vital capacity. (B) DLCO=diffusing capacity of the lung for carbon monoxide. (C) 6MWD=6-min walk distance. (D) TLC=total lung capacity. (E) FEV₁. Note that FVC, TLC, and FEV₁ were assessed in post-hoc analyses.

multiple imputation; appendix 1, p 3). The imputation of missing values by either SSD or LOCF had a similar effect on the time-dependent change in FVC % predicted for both groups (figure 2; a comparison with complete

cases and all three imputation methods, including multiple imputation, is in appendix 1, p 14). Omittance of data from deceased patients resulted in a loss of significance for all tested models regardless of imputation method when the rank ANCOVA was applied (appendix 1 p 3). The sensitivity analysis done in the per-protocol population included 46 patients in the pirfenidone group and 50 in the placebo group, who had no documented major protocol deviations or any serious adverse events. For this analysis, the Hodges-Lehmann estimate for median difference in FVC % predicted between groups was 2.61 (95% CI -0.40 to 5.12). Because the p value exceeded the 5% significance level in the rank ANCOVA-based analysis of the primary endpoint when testing the entire per-protocol population ($p=0.092$) and when testing the per-protocol population stratified for diagnostic group ($p=0.065$; appendix 1, p 3), no further hypotheses on subgroups were tested.

In addition, the pre-specified sensitivity analysis of FVC slopes using linear mixed-model repeated measures analyses showed a significantly reduced decline in the FVC % predicted slope in the pirfenidone group versus the placebo group, which was independent of imputation of missing values for deceased patients ($p=0.037$ with the prespecified imputation method, $p=0.047$ for raw data without imputation; appendix 1, p4). Estimated slope differences between the pirfenidone and placebo groups from baseline to week 48 were 3.53 FVC % predicted (95% CI 0.21–6.86) with the prespecified imputation method, and 2.79 FVC % predicted (95% CI 0.03–5.54) without imputation of missing data (appendix 1, p 16).

In post-hoc analyses for absolute changes in FVC, FEV₁, and TLC (without imputation of missing values), the treatment effect of pirfenidone at week 48 was not significantly different to that of placebo (table 2, figure 3). Group differences in the open label extension phase of the study appeared consistent with the primary endpoint findings, although low patient numbers and short trial duration prevented statistical analysis (appendix 1, p 17). The additional inclusion of sex and oxygen supply at baseline as covariates in post-hoc sensitivity analyses with the rank ANCOVA model did not notably alter the results of our hierarchical testing procedure (data not shown).

Discussion

In the RELIEF trial, we investigated the efficacy and safety of pirfenidone in four well characterised ILD entities, in which patients had FVC decline despite conventional therapy before enrolment, indicative of a progressive fibrotic phenotype. Our study population might therefore be viewed as a representative cohort of what is currently categorised as progressive fibrotic ILD. The final analysis of the full data set revealed that, according to the prespecified statistical analysis and imputation rules, patients who received pirfenidone had a slower decline of

FVC % predicted from baseline to 48 weeks than those who received placebo. The per-protocol analysis of the primary outcome and analysis of secondary outcomes undertaken without imputation were all non-significant, except for DLCO. However, the findings need to be interpreted carefully in the context of the early termination of the trial.

Owing to the complexity of the study, including the need for documented progression, patient recruitment was slow, even after increasing the DLCO inclusion criterion from 25–75% predicted to 10–90% predicted. The interim analysis therefore resulted in early termination of the trial because of futility and withdrawal of all patients from the study drug as instructed by the central ethics committee. Given the substantially reduced sample size compared with the initial study design and the non-significant results of the sensitivity analyses and most secondary analyses when deceased patients had been excluded, the significant treatment effect we observed might be partly attributable to the unevenly distributed deaths among patients between the treatment and placebo groups.

However, in view of the early stopping of the trial, there was an unforeseen increase in the mechanisms as well as the proportions of missing data (data for 47% of all patients needed to be imputed); these types of missing data differed from those considered initially and required specific analyses. Although deaths (particularly if respiratory driven) will show greater than average decline in FVC (and therefore cannot be considered missing at random), in this case the most common reason for missing values was study termination, which affected all patients who were still under treatment at that time without distinction; therefore, these values can be considered as missing at random and thus should not introduce bias. The two additional post-hoc sensitivity analyses using different imputation methods for the rank ANCOVA-based analysis of the primary endpoint to address the changes in missing data mechanisms suggested a significant effect of pirfenidone in surviving patients.

Moreover, integration of longitudinal data for patients for whom the week 48 measurement was missing by mixed-model repeated measures slope analysis with and without imputation showed consistent results in favour of pirfenidone. This finding, added to the secondary analyses of DLCO, and the fact that the treatment effect appeared to be significant and robust independent of the three applied imputation models support the interpretation of the prespecified primary endpoint analysis that FVC decline was less pronounced in the pirfenidone group. Because of the small number of patients, subgroup analyses were deemed uninformative.

Additionally, the safety and tolerability profile of pirfenidone was similar to that described in previous IPF trials^{6,7} despite ongoing anti-inflammatory therapy in the population under study. Notably, imbalances in overall

	Pirfenidone (n=64)	Placebo (n=63)	Total number of SAEs (n=64)	Total number of patients with ≥1 SAE (n=127)
Number of patients with SAEs	26 (41%)	35 (56%)	..	61 (48%)
Infections and infestations	5 (8%)	10 (16%)	15	15 (12%)
General disorders and administration site conditions including disease worsening	2 (3%)	7 (11%)	10	9 (7%)
Respiratory, thoracic, and mediastinal disorders	4 (6%)	4 (6%)	9	8 (6%)
Surgical and medical procedures	4 (6%)	2 (3%)	7	6 (5%)
Cardiac disorders	1 (2%)	5 (8%)	6	6 (5%)
Neoplasms benign, malignant, and unspecified (with cysts or polyps)	2 (3%)	3 (5%)	5	5 (4%)
Injury, poisoning, or procedural complications	1 (2%)	2 (3%)	3	3 (2%)
Investigations	1 (2%)	1 (2%)	2	2 (2%)
Nervous system disorders	2 (3%)	0 (0%)	2	2 (2%)
Musculoskeletal and connective tissue disorders	2 (3%)	0 (0%)	2	2 (2%)
Renal and urinary disorders	1 (2%)	1 (2%)	2	2 (2%)
Gastrointestinal disorders	1 (2%)	0 (0%)	1	1 (1%)
Deaths*	1 (2%)	5 (8%)	..	6 (5%)

Data are n (%) or n. SAEs=serious adverse events. All SAEs are listed according to System Organ Class in the Medical Dictionary for Regulatory Activities, version 22.1 (a full listing of preferred terms is in appendix 1, pp 8-9). *3/5 placebo deaths and 0/5 of pirfenidone deaths were respiratory-related.

Table 3: Incidence of serious adverse events at the level of System Organ Class

mortality and respiratory tract infections captured as severe adverse events and adverse events numerically favoured pirfenidone.

Although smaller in absolute numbers, the observed relative treatment effects were in a similar range as those observed in clinical trials with pirfenidone in patients with IPF^{6,7} and in patients with progressive unclassifiable ILD,⁸ and are also in line with clinical trials with nintedanib in ILD associated with systemic sclerosis (SENSCIS)⁴ and with various progressive fibrotic ILDs (INBUILD trial),⁵ all showing favourable outcomes under antifibrotic treatment. The FVC decline in the placebo group in our study was only -114.4 mL, which is considerably less than in INBUILD⁵ (-211.0 mL overall and -154.2 mL in patients with patterns of non-usual interstitial pneumonia on high-resolution CT), which included a related, but not identical patient population. Potential reasons for this observation include the ILD subtype distribution (the marked difference in FVC decline between patients with usual and non-usual interstitial pneumonia) and the handling of concomitant medication (which was largely permitted in RELIEF, but mainly restricted to <20 mg steroid per day in INBUILD).

The progressive fibrosing phenotype was differently defined in all trials of pirfenidone and nintedanib, and there is an ongoing discussion around which criteria might be the most practical and eventually predictive for

the progressive fibrotic ILD phenotype. Our definition of an annual FVC decline of more than 5% predicted based on three spirometric measurements turned out to be robust, but might be somewhat impractical in current clinical practice. This criterion, although helpful in safely identifying patients with progressive disease, also contributed significantly to our inability to fully recruit our study population. In clinical practice, assessing progression in progressive fibrotic ILD is a multidisciplinary exercise, aiming to integrate symptoms, pulmonary function, and imaging. Therefore, the approach taken in the INBUILD study⁵ of combining at least two criteria of progression appears attractive. For the future, however, it would be most desirable to use predictive biomarkers at first diagnosis to predict the progressive fibrotic ILD phenotype.

Possible explanations for the apparently broader efficacy of pirfenidone or nintedanib beyond IPF include early and late pro-fibrotic events and mechanisms shared by IPF and other, non-IPF, progressive fibrotic ILDs. Among these, therapeutic blockade of increased alveolar epithelial transforming growth factor (TGF)- β formation due to chronic epithelial injury that is also consistently found in CTD-ILD, chronic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, and asbestos-induced lung fibrosis^{13,14} might play a role. The explanations might also include blockade of mechanisms of self-perpetuation of fibrosis, such as release of TGF- β via the α -v-integrin or permanent STAT3 activation due to enhanced stiffness of the matrix,^{15,16} or to extensive epigenetic changes occurring in lung myofibroblasts presumably due to the long-lasting activation.¹⁷ The number of respiratory infections captured as serious adverse events and adverse events was lower in the pirfenidone group than in the placebo group, possibly linked to TGF- β blockade in a cohort in which around 70% of all patients were on a single or combined immunosuppressive drug treatment. A previous review¹⁸ highlighted that TGF- β signalling has been shown to result in increased susceptibility to bacterial or viral stressors. As immunosuppressive treatment modalities similarly result in an enhanced susceptibility of patients towards infection, it is conceivable that blockade of TGF- β by pirfenidone might have helped to reduce susceptibility to infection in immunosuppressant-treated patients, whereas such an approach in a separate study⁷ did not change the rate of respiratory infections in patients with IPF who were not treated with steroids or immunosuppressants.

Although our results showed a consistent trend in better outcomes and preserved lung function in the pirfenidone group, we nevertheless acknowledge the limitations of our study. Most importantly, an interim analysis undertaken because of the slow recruitment rate resulted in early termination of the trial. The decisions to do the interim analysis and—as a consequence—stop the study might be criticised in retrospect but they were driven by several considerations: (1) the very low rate of recruitment, (2) initiation of competing trials in the face

of limited funding of our study, further limiting patient recruitment, and (3) the analysis predicting that a positive outcome was very improbable. This obviously caused a failure to achieve the intended power, and caused a high number of missing values as patients did not finish the trial as planned. Nevertheless, analyses of the primary study endpoint—including those with the prespecified imputation methods for missing values as well as additional post-hoc imputation models—showed a treatment effect, whereas secondary and sensitivity analysis undertaken without imputation were found to be non-significant, except for DLCO.

In summary, we showed that treatment of patients with progressive fibrotic ILDs other than IPF with pirfenidone is safe, with the side-effect profile being similar to that reported in IPF trials. Additionally, our data suggest that treatment with pirfenidone in addition to ongoing medication might attenuate disease progression as measured by loss of FVC, and might be a reasonable strategy for these patients. However, because of the premature termination of our study and the resulting limitations with regard to patient numbers and missing values, these results should be interpreted with caution.

Contributors

The research concept of the study was developed by JB and AG. All authors undertook the study. PN conceptualised the statistical analyses, calculated the sample size, and implemented the imputation of missing values. JJ did the statistical analysis. JB, AG, and JJ accessed and verified the data. JB and AG wrote the first draft of the manuscript. All authors participated in the development and finalisation of the manuscript and vouch for the trial's fidelity to the protocol. All authors had full access to all the data in the study. JB and AG had final responsibility for the decision to submit for publication.

Declaration of interests

JB reports personal fees from Boehringer Ingelheim, Bristol Myers Squibb (BMS), Biogen, Galapagos, Promedior, Roche, and the German Center for Lung Research (DZL). SB reports personal fees and non-financial support from Roche, Bayer, Novartis, and Boehringer Ingelheim; personal fees from Merck Serono; and non-financial support from Teva, Gilead, Lucane Pharma, Actelion, CSL Behring, and Vertex. FB reports personal fees for consultancy, lecturing, and travel support from Boehringer Ingelheim and Roche. MC reports grants from DZL. JHF reports personal fees, grants, and non-financial support from Roche; and personal fees and non-financial support from Boehringer Ingelheim. AG reports grants from DZL, Boehringer Ingelheim, and Roche. MH reports grants from Actelion; honoraria for lectures from Actelion, Bayer Healthcare, Berlin Chemie, Boehringer Ingelheim, GlaxoSmithKline (GSK), Merck Sharp & Dohme (MSD), Novartis, OMT, Pfizer, and Roche; honoraria for advisory boards from Actelion, Bayer, Boehringer Ingelheim, GSK, MSD, Roche; and honoraria for clinical trials from Actelion, Bayer, GSK, Pfizer, and United Therapeutics. NK reports personal fees from Roche. DK reports personal fees from Roche; and personal fees and non-financial support from Boehringer Ingelheim. MK reports grants from DZL; and grants and personal fees from Boehringer Ingelheim and Roche. AP reports grants from DZL; grants, personal fees, and non-financial support from Boehringer Ingelheim and AstraZeneca; personal fees and non-financial support from Roche, Pliant, Chiesi Pharmaceuticals, and Nitto Denko; personal fees from Amgen; and non-financial support from Galapagos. KFR reports grants and personal fees from Boehringer Ingelheim and AstraZeneca; and personal fees from Novartis, Sanofi, Regeneron, Roche, and Chiesi Pharmaceuticals. TW reports grants from Roche; and personal fees from Boehringer Ingelheim, Roche, and Novartis. HWil reports personal fees for lectures or consultations from Actelion–Janssen, Bayer, Biotest, Boehringer Ingelheim, GSK, Pfizer, and Roche.

HWir reports lecture fees from Roche. All other authors declare no competing interests.

Data sharing

We will make anonymised individual participant data available to the scientific community with as few restrictions as feasible, while retaining exclusive use until the publication of major outcomes. Data requests from qualified researchers should be submitted to JB (juergen.behr@med.uni-muenchen.de) for consideration.

Acknowledgments

This study was funded by the German Center for Lung Research and Roche Pharma AG (Roche Pharma AG also provided the study drugs). The Center for Clinical Trials of the University of Marburg was responsible for biometry, coordination, and conduct of the trial. We thank our patients and their families for their participation in the study. We also thank the independent data monitoring committee members in Germany: Ralf Ewert (Greifswald), Detlef Kirsten (Grosshansdorf), and David Petroff (Leipzig), none of whom had a conflict of interest with the study; and all other colleagues who were involved in this trial and who are mentioned in the complete list of investigators and co-workers of the RELIEF study (appendix 1, p 1).

References

- Meyer KC. Diagnosis and management of interstitial lung disease. *Transl Respir Med* 2014; **2**: 4.
- Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018; **378**: 1811–23.
- Barnikel M, Million P, Knoop H, Behr J. The natural course of lung function decline in asbestos exposed subjects with pleural plaques and asbestosis. *Respir Med* 2019; **154**: 82–85.
- Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; **380**: 2518–28.
- Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; **381**: 1718–27.
- Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; **377**: 1760–69.
- King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; **370**: 2083–92.
- Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020; **8**: 147–57.
- Behr J, Neuser P, Prasse A, et al. Exploring efficacy and safety of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF)—a randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial. *BMC Pulm Med* 2017; **17**: 122.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979: 549–56.
- Wickham H. ggplot2. Elegant graphics for data analysis. New York: Springer, 2016.
- R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing,; 2020.
- Kamp DW, Liu G, Cheresch P, et al. Asbestos-induced alveolar epithelial cell apoptosis. The role of endoplasmic reticulum stress response. *Am J Respir Cell Mol Biol* 2013; **49**: 892–901.
- Korfei M, von der Beck D, Henneke I, et al. Comparative proteome analysis of lung tissue from patients with idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP) and organ donors. *J Proteomics* 2013; **85**: 109–28.
- Froese AR, Shimbori C, Bellay P-S, et al. Stretch-induced activation of transforming growth factor- β 1 in pulmonary fibrosis. *Am J Respir Crit Care Med* 2016; **194**: 84–96.
- Oh RS, Haak AJ, Smith KM, et al. RNAi screening identifies a mechanosensitive ROCK-JAK2-STAT3 network central to myofibroblast activation. *J Cell Sci* 2018; **131**: jcs209932.
- Korfei M, Skwarna S, Henneke I, et al. Aberrant expression and activity of histone deacetylases in sporadic idiopathic pulmonary fibrosis. *Thorax* 2015; **70**: 1022–32.
- Sanjabi S, Oh SA, Li MO. Regulation of the immune response by TGF- β : from conception to autoimmunity and infection. *Cold Spring Harb Perspect Biol* 2017; **9**: a022236.