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BRIEF REPORT

Pirfenidone in Unclassifiable Interstitial Lung Disease: A Subgroup Analysis by Concomitant Mycophenolate Mofetil and/or Previous Corticosteroid Use

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ABSTRACT

Introduction: There are currently no approved treatments solely for unclassifiable interstitial lung disease (uILD); however, a recent trial showed this population can benefit from pirfenidone. We report a subgroup analysis of this trial to assess the effects of immunomodulators (concomitant mycophenolate mofetil [MMF] and/or previous corticosteroids) with pirfenidone in patients with uILD.

Methods: This was a multicenter, international, double-blind, randomized, placebo-controlled phase II trial of patients with progressive fibrosing uILD (NCT03099187). Patients were randomized (1:1) to receive pirfenidone

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2403 mg/day or placebo. This analysis assessed forced vital capacity (FVC) change from baseline measured using site spirometry (key secondary endpoint) and safety over 24 weeks by concomitant MMF use at randomization (prespecified analysis) and/or previous corticosteroid use (post hoc analysis).

Results: Overall, 253 patients were randomized, including 45 (17.8%) patients (pirfenidone, $n = 23$; placebo, $n = 22$) receiving concomitant MMF with/without previous corticosteroids (MMF subgroup); 79 (31.2%) patients (pirfenidone, $n = 44$; placebo, $n = 35$) receiving previous corticosteroids without MMF (corticosteroids/no-MMF subgroup); and 129 (51.0%) patients (pirfenidone, $n = 60$; placebo, $n = 69$) not receiving concomitant MMF or previous corticosteroids (no-corticosteroids/no-MMF subgroup). At 24 weeks, difference in mean (95% confidence interval) FVC change from baseline between pirfenidone and placebo was − 55.4 mL (− 206.7, 96.0; $P = 0.4645$) in the MMF subgroup; 128.4 mL (− 6.4, 263.3; $P = 0.0617$) in the corticosteroids/no-MMF subgroup; and 115.5 mL (35.1, 195.9; $P = 0.0052$) in the no-corticosteroids/no-MMF subgroup. All subgroups generally exhibited a similar pattern of treatment-emergent adverse events.

Conclusion: Although limited by design and small sample sizes, this analysis suggests pirfenidone may be less effective in patients with uILD receiving concomitant MMF, whereas a beneficial treatment effect was observed in patients not receiving concomitant MMF regardless of previous corticosteroid use. Pirfenidone was well tolerated regardless of MMF and/or corticosteroid use.

Trial Registration Number: ClinicalTrials.gov: NCT03099187.

Keywords: Corticosteroid; Immunomodulator; Mycophenolate mofetil; Pirfenidone; Unclassifiable interstitial lung disease

Key Summary Points

Why carry out this study?

Diagnosis of a specific interstitial lung disease (ILD) is important for identifying the most appropriate management strategy and informing disease prognosis; however, despite thorough investigation by a multidisciplinary team, some patients are diagnosed with unclassifiable ILD (uILD).

There are currently no approved treatments solely indicated for uILD; however, a recent 24-week phase II clinical trial that evaluated the efficacy and safety of pirfenidone versus placebo in patients with progressive fibrotic uILD suggested that this population of patients can benefit from pirfenidone treatment.

The subgroup analysis of this phase II clinical trial aimed to assess the effects of immunomodulators (concomitant mycophenolate mofetil [MMF] and/or previous corticosteroids) with pirfenidone in patients with uILD.

What was learned from the study?

Despite the limitation of a small sample size, this subgroup analysis suggests that pirfenidone may be less effective in patients with uILD receiving MMF at randomization, whereas a beneficial treatment effect for pirfenidone on forced vital capacity change was observed in patients not receiving MMF at randomization regardless of previous corticosteroid use; pirfenidone was well tolerated regardless of MMF and/or corticosteroid use.

Further research is needed to explore these findings in a larger group of patients in a study appropriately designed to determine the effects of concomitant immunomodulators with pirfenidone in patients with progressive uILD.

INTRODUCTION

Interstitial lung diseases (ILDs) are a large, heterogeneous group of diseases characterized by abnormalities of pulmonary interstitium or alveoli, including fibrosis [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 [2], the clinical course of other ILDs is variable [1, 3, 4].

Diagnosis of a specific ILD is important for identifying the most appropriate management strategy and informing disease prognosis [1, 3, 4]. However, despite thorough investigation by a multidisciplinary team, some patients are diagnosed with unclassifiable ILD (uILD) due to nonspecific or conflicting clinical, radiological, or histopathological findings or where invasive diagnostic procedures are inappropriate or not possible [1, 3, 4]. Adding to the heterogeneity of the uILD population is a subgroup of patients that meet criteria for the research classification scheme of interstitial pneumonia with autoimmune features (IPAF), who often fall within the category of uILD [3, 5].

Small retrospective cohort studies and a case study have shown potential benefits of immunomodulators including mycophenolate mofetil (MMF) and corticosteroids in some patients with IPAF [6–9] or other uILDs [10]. Moreover, immunomodulators are frequently used as concomitant medications in patients with fibrosing ILDs in clinical studies or in clinical practice [11–13].

There are currently no approved treatments solely indicated for uILD, but nintedanib is now approved for progressive fibrosing ILDs, including uILD, on the basis of its efficacy and safety demonstrated in the INBUILD study [12, 14]. Moreover, a recent 24-week phase II clinical trial that evaluated the efficacy and safety of pirfenidone versus placebo in patients with progressive fibrotic uILD suggested that this population of patients can benefit from antifibrotic treatment with pirfenidone [15]. It should be noted that the primary endpoint (forced vital capacity [FVC] measured by home spirometry) could not be analyzed in this trial because of technical and analytical issues with home spirometry. Therefore, the beneficial effect of pirfenidone in patients with uILD was based on the analysis of the key secondary endpoints, including change in FVC measured by site spirometry, an outcome which has been utilized as a primary endpoint in clinical trials for IPF [16, 17] and other progressive fibrosing ILDs [14, 18]. Moreover, pirfenidone treatment was efficacious and well tolerated in patients with other non-IPF progressive fibrosing ILDs, including connective tissue disease-associated ILD, fibrotic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis, and asbestos-induced lung fibrosis, in the RELIEF trial [18].

Here, we report a subgroup analysis of the phase II trial of pirfenidone in patients with uILD to assess the effects of immunomodulators (concomitant MMF and/or previous corticosteroids) with pirfenidone in these patients.

METHODS

This was a multicenter, international, double-blind, randomized, placebo-controlled phase II trial of patients with progressive fibrosing uILD (ClinicalTrials.gov: NCT03099187), the methods of which have been previously described [15, 19]. 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.

Patients were randomized in a 1:1 ratio to receive pirfenidone 2403 mg/day or placebo. Randomization was stratified by concomitant MMF use. Patients were permitted to receive a maximum MMF dose of 1.5 g twice daily; otherwise, the dosage was at the discretion of the investigator. Patients who were not taking MMF at the time of enrollment were not permitted to start MMF during the trial. Patients were not permitted to receive any other immunomodulators during the trial or to

receive treatment with high-dose systemic corticosteroids (i.e., more than 15 mg/day of prednisolone or equivalent) for more than 4 weeks during the trial.

The primary endpoint was predicted mean change in FVC (in milliliters) measured using daily home spirometry over 24 weeks. As previously reported, the primary endpoint could not be analyzed because of technical issues with the home spirometers and the inclusion of patients with a small number of readings collected within a short time window [15]. Examples of FVC readings recorded at home included daily values of less than 0.5 L or greater than 6 L, and predicted increases of 33 L at 24 weeks, which are clearly impossible. As the statistical assumptions for applying a Student's *t* test could not be fulfilled, the pre-specified model could not be applied to the home spirometry data [15]. Secondary endpoints included change in FVC from baseline measured by spirometry during clinic visits, change in percentage predicted carbon monoxide diffusing capacity (DLco) from baseline, and change in 6-min walk distance (6MWD) from baseline.

Primary and secondary efficacy endpoints were assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients. Safety was assessed in the safety analysis set (SAS), which included all randomly assigned patients who received at least one dose of study drug. The incidence and severity of treatment-emergent adverse events (TEAEs) and withdrawals from study treatment or study discontinuations were recorded.

In this subgroup analysis, we investigated baseline characteristics, changes in FVC (in milliliters and percentage predicted) from baseline measured using site spirometry, change in percentage predicted DLco from baseline, change in 6MWD from baseline, and safety by concomitant MMF use at randomization (pre-specified analysis), and/or previous corticosteroid use (all patients who started corticosteroids prior to or at baseline; post hoc analysis), all over 24 weeks. It should be noted that patients who received corticosteroids after baseline were not included in the analyses because those patients started treatment at different times and for different durations, which may have confounded the results of the analyses.

The change in FVC (percentage predicted and in milliliters) between baseline and week 24 measured by site spirometry was estimated from a linear regression model. The mean change in FVC was compared between treatment groups using a Student's *t* test with a two-sided significance level of 5%. Changes in percentage predicted FVC, percentage predicted DLco, and 6MWD were compared between treatment groups using a rank analysis of variance model, with change from baseline used as an outcome variable and standardized rank baseline value used as a covariate. Categorical changes in percentage predicted FVC (greater than 5% and greater than 10%) were compared between treatment groups using a Cochran–Mantel–Haenszel test. Categorical changes in percentage predicted DLco (greater than 15%) were compared between treatment groups using logistic regression or Fisher's exact test, where appropriate. Categorical changes in 6MWD (greater than 50 m) were compared between treatment groups using logistic regression.

RESULTS

Overall, 253 patients were randomized and included in the ITT analysis set (pirfenidone, $n = 127$; placebo, $n = 126$). The SAS included 251 patients (pirfenidone, $n = 127$; placebo, $n = 124$). The present analysis included 45 (17.8%) patients (pirfenidone, $n = 23$; placebo, $n = 22$) who received concomitant MMF treatment with or without previous corticosteroid treatment (MMF subgroup), 79 (31.2%) patients (pirfenidone, $n = 44$; placebo, $n = 35$) who received previous corticosteroid treatment without MMF (corticosteroids/no-MMF subgroup), and 129 (51.0%) patients (pirfenidone, $n = 60$; placebo, $n = 69$) who received no concomitant MMF treatment or previous corticosteroid treatment (no-corticosteroids/no-MMF subgroup). In total, 21 (91.3%) and 17 (77.3%) patients receiving concomitant MMF treatment also received concomitant corticosteroid treatment during the double-blind period in the pirfenidone and placebo groups, respectively.

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

	Pirfenidone			Placebo		
	MMF (with or without corticosteroids) (n = 23)	**Corticosteroids/ no MMF (n = 44)**	**No corticosteroids/no MMF (n = 60)**	**MMF (with or without corticosteroids) (n = 22)**	**Corticosteroids/ no MMF (n = 35)**	**No corticosteroids/no MMF (n = 69)**
Age at screening, years	63.4 (10.1)	67.1 (10.5)	70.4 (9.1)	67.1 (9.7)	67.7 (10.2)	67.8 (8.6)
Sex, n (%)						
Male	14 (60.9)	24 (54.5)	32 (53.3)	13 (59.1)	21 (60.0)	35 (50.7)
Female	9 (39.1)	20 (45.5)	28 (46.7)	9 (40.9)	14 (40.0)	34 (49.3)
Race, n (%)						
White	21 (91.3)	43 (97.7)	56 (93.3)	22 (100.0)	33 (94.3)	68 (98.6)
Black	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.9)	1 (1.4)
Asian	2 (8.7)	1 (2.3)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Body mass index, kg/m^2	30.8 (6.0)	30.1 (6.7)	29.8 (5.7)	30.2 (5.6)	28.9 (5.3)	29.3 (5.3)
Percentage predicted FVC, %	68.7 (18.1)	68.2 (17.5) (n = 43)	80.6 (18.0) (n = 59)	72.6 (12.4)	66.7 (17.0) (n = 34)	79.0 (20.8)
Percentage predicted DLco, %	43.9 (9.5) (n = 22)	45.3 (13.2) (n = 40)	49.0 (11.2) (n = 57)	46.4 (11.2) (n = 21)	48.0 (13.8) (n = 32)	51.8 (13.8) (n = 64)
Percentage predicted FEV_1, %	72.4 (16.8)	70.5 (17.5) (n = 43)	83.6 (18.5) (n = 58)	78.0 (14.6)	71.2 (20.9) (n = 34)	82.0 (21.3)

Table 1 continued

	Pirfenidone			Placebo		
	MMF (with or without corticosteroids) (n = 23)	Corticosteroids/no MMF (n = 44)	No corticosteroids/no MMF (n = 60)	MMF (with or without corticosteroids) (n = 22)	Corticosteroids/no MMF (n = 35)	No corticosteroids/no MMF (n = 69)
FEV_1/FVC ratio	0.8 (0.1)	0.8 (0.1) (n = 43)	0.8 (0.1) (n = 58)	0.8 (0.1)	0.8 (0.1) (n = 34)	0.8 (0.1)
6MWD, m	412.6 (119.5)	396.5 (106.5)	380.0 (119.5)	373.5 (93.2)	394.1 (105.7)	400.5 (114.2)

Data are mean (SD) unless otherwise specified

6MWD 6-min walk distance, *DLco* carbon monoxide diffusing capacity, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *MMF* mycophenolate mofetil, *SD* standard deviation

Overall, 33 patients in the study had an IPAF diagnosis (pirfenidone, n = 15 and placebo, n = 18); 12 of these patients were in the MMF subgroup (pirfenidone, n = 6; placebo, n = 6).

Demographics and baseline characteristics of the ITT population are shown in Table 1. Demographics were similar between all concomitant MMF and previous corticosteroid subgroups (mean age 63.4–70.4 years; male 50.7–60.9%; white race 91.3–100.0%). Mean percentage predicted FVC at baseline measured by site spirometry was similar between the MMF subgroup (68.7–72.6%) and corticosteroids/no-MMF subgroup (66.7–68.2%) but was slightly higher in the no-corticosteroids/no-MMF subgroup (79.0–80.6%). Mean percentage predicted DLco (43.9–51.8%) and mean 6MWD (373.5–412.6 m) at baseline were similar between all concomitant MMF and previous corticosteroid subgroups.

At 24 weeks, the mean (95% confidence interval [CI]) predicted FVC change from baseline was − 132.8 mL (− 253.2, − 12.4) in the pirfenidone group and − 77.5 mL (− 176.6, 21.6) in the placebo group for the MMF subgroup (difference − 55.4 mL [− 206.7, 96.0]; P = 0.4645); − 16.5 mL (− 100.7, 67.7) in the pirfenidone group and − 144.9 mL (− 256.7, − 33.2) in the placebo group for the corticosteroids/no-MMF subgroup (difference 128.4 mL [− 6.4, 263.3]; P = 0.0617); and 12.8 mL (− 54.1, 79.7) in the pirfenidone group and − 102.7 mL (− 151.5, − 53.8) in the placebo group for the no-corticosteroids/no-MMF subgroup (difference 115.5 mL [35.1, 195.9]; P = 0.0052; Fig. 1). Categorical change in FVC of greater than 5% or greater than 10%, change in percentage predicted DLco, and change in 6MWD by concomitant MMF and previous corticosteroid use are shown in Table 2.

Generally, a similar pattern of TEAEs was observed across all subgroups (Table 3). The incidence of treatment-related TEAEs was slightly higher in the MMF subgroup (82.6%) than the other subgroups (68.2–68.3%) for pirfenidone-treated patients. The incidence of treatment-related TEAEs was lower in the corticosteroids/no-MMF subgroup (37.1%) than in the other subgroups (49.3–50.0%) for placebo-treated patients. Additionally, higher

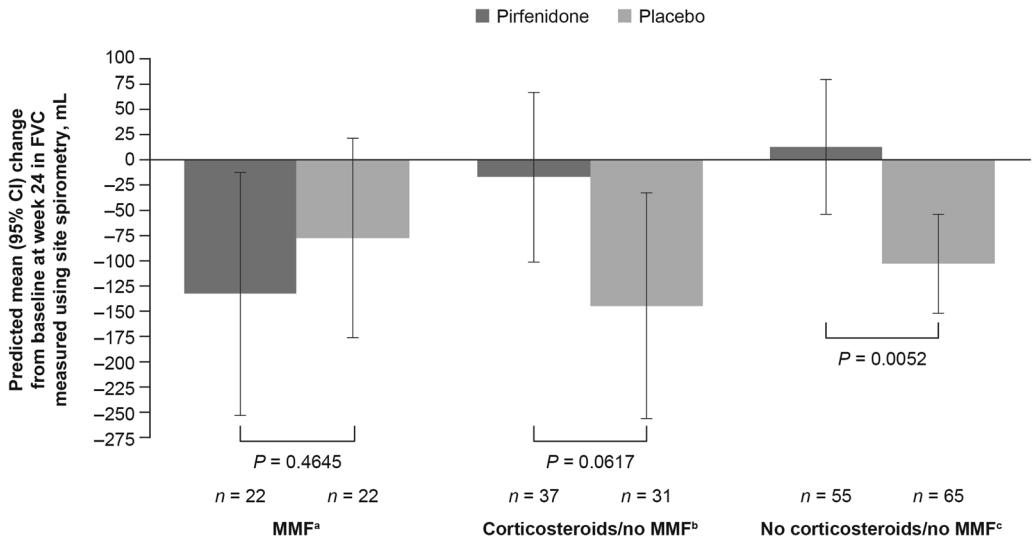

Fig. 1 Mean (95% CI) change from baseline to week 24 in FVC (measured by site spirometry) for pirfenidone versus placebo by concomitant MMF use at randomization and/or previous corticosteroid use. FVC (mL) decline at week 24 measured by site spirometry and estimated from linear regression model. Two-sided 95% CI for mean value is based on percentiles of the *t* distribution. *CI* confidence interval, *FVC* forced vital capacity, *MMF* mycophenolate mofetil. [a]Patients who received concomitant MMF at randomization with/without corticosteroids prior to or at baseline. [b]Patients who received corticosteroids prior to or at baseline without concomitant MMF at randomization. [c]Patients who did not receive corticosteroids prior to or at baseline or concomitant MMF at randomization

proportions of serious TEAEs (25.7%) and severe TEAEs (31.4%) were observed in the placebo group for the corticosteroids/no-MMF subgroup than in the other subgroups (serious TEAEs, 9.1–11.9%; severe TEAEs, 9.1–19.4%). Gastrointestinal (GI) disorders were more frequent in the MMF subgroup than in the other subgroups in both the pirfenidone (69.6% vs 47.7–58.3%) and placebo (54.5% vs 31.4–40.3%) groups.

DISCUSSION

Although the overall results of the uILD study suggested that patients with progressive fibrosing uILD can benefit from pirfenidone over 24 weeks, this subgroup analysis suggests that pirfenidone may be less effective in patients receiving concomitant MMF at randomization versus those not receiving MMF. A numerically beneficial treatment effect for pirfenidone versus placebo on FVC change was observed regardless of previous corticosteroid use in patients not receiving MMF, although the beneficial effect in the corticosteroids/no-MMF subgroup was not statistically significant. This was most likely as a result of small samples sizes and because the study was not designed nor powered to show differences between corticosteroid subgroups. It is important to note that although the patient demographics and clinical characteristics were generally similar irrespective of concomitant MMF and/or previous corticosteroid use, mean percentage predicted FVC at baseline was higher in the no-corticosteroids/no-MMF subgroup compared with the MMF and corticosteroids/no-MMF subgroups. This difference in FVC at baseline may have contributed to the lack of statistically significant effect of pirfenidone on FVC decline in the MMF and corticosteroids/no-MMF subgroups versus the no-corticosteroids/no-MMF subgroup. In general, FVC measurements can be highly variable between patients, and small sample sizes can lead to large CIs, which were also observed in these analyses. Variable FVC measurements suggest that efficacy may differ depending on patients' genotype and/or phenotype, and as

Table 2 Efficacy outcomes at week 24 in the intention-to-treat population (n = 253)

	MMF (with or without corticosteroids)			Corticosteroids/no MMF			No corticosteroids/no MMF		
	Pirfenidone (n = 23)	Placebo (n = 22)	Pirfenidone vs placebo	Pirfenidone (n = 44)	Placebo (n = 35)	Pirfenidone vs placebo	Pirfenidone (n = 60)	Placebo (n = 69)	Pirfenidone vs placebo
FVC change from baseline measured by site spirometry, % predicted									
P value (rank ANCOVA)	–	–	$P = 0.3251$	–	–	$P = 0.0175$	–	–	$P = 0.0351$
Patients with > 5% decline in FVC	10 (43.5)	12 (54.5)	0.64 (0.20, 2.07); $P = 0.4617$[a]	16 (36.4)	18 (51.4)	0.55 (0.22, 1.34); $P = 0.1878$[a]	21 (35.0)	43 (62.3)	0.34 (0.16, 0.69); $P = 0.0028$[a]
Patients with > 10% decline in FVC	5 (21.7)	5 (22.7)	0.93 (0.22, 3.85); $P = 0.9219$[a]	5 (11.4)	11 (31.4)	0.29 (0.09, 0.93); $P = 0.0311$[a]	8 (13.3)	17 (24.6)	0.47 (0.19, 1.19); $P = 0.1102$[a]
DLco change from baseline, % predicted									
P value (rank ANCOVA)	–	–	$P = 0.0480$	–	–	$P = 0.1366$	–	–	$P = 0.0518$
Patients with > 15% decline in DLco	1 (4.3)	1 (4.5)	0.95 (0.06, 16.27); $P = 0.9743$[b]	1 (2.3)	2 (5.7)	$P = 0.5813$[c]	0 (0.0)	9 (13.0)	$P = 0.0035$[c]
6MWD change from baseline, m									
P value (rank ANCOVA)	–	–	$P = 0.3295$	–	–	$P = 0.1946$	–	–	$P = 0.0162$
Patients with > 50 m decline in 6MWD	11 (47.8)	4 (18.2)	4.12 (1.06, 16.03); $P = 0.0408$[b]	9 (20.5)	7 (20.0)	1.03 (0.34, 3.11); $P = 0.9602$[b]	14 (23.3)	24 (34.8)	0.57 (0.26, 1.24); $P = 0.1570$[b]

Data are *n* (%) unless otherwise specified

6MWD 6-min walk distance, *ANCOVA* analysis of variance, *CI* confidence interval, *DLco* carbon monoxide diffusing capacity, *FVC* forced vital capacity, *MMF* mycophenolate mofetil

[a]Odds ratio (95% CI), *P* value from Cochran–Mantel–Haenszel test stratified by randomization stratification factors

[b]Odds ratio (95% CI), *P* value from logistic regression

[c]*P* value from Fisher's exact test

Table 3 TEAEs in the safety analysis set (n = 251)

	Pirfenidone			Placebo		
	MMF (with or without corticosteroids) (n = 23)	Corticosteroids/ no MMF (n = 44)	No corticosteroids/ no MMF (n = 60)	MMF (with or without corticosteroids) (n = 22)	Corticosteroids/ no MMF (n = 35)	No corticosteroids/ no MMF (n = 67)
Any TEAEs	22 (95.7)	43 (97.7)	55 (91.7)	19 (86.4)	27 (77.1)	55 (82.1)
Any treatment-related TEAEs	19 (82.6)	30 (68.2)	41 (68.3)	11 (50.0)	13 (37.1)	33 (49.3)
Any serious TEAEs	5 (21.7)	5 (11.4)	8 (13.3)	2 (9.1)	9 (25.7)	8 (11.9)
Any treatment-related serious TEAEs	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.5)
Any severe TEAEs	5 (21.7)	10 (22.7)	14 (23.3)	2 (9.1)	11 (31.4)	13 (19.4)
Any treatment-related severe TEAEs	0 (0.0)	4 (9.1)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.0)
TEAEs of special interest[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to death	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.5)
Treatment-related TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation	4 (17.4)	9 (20.5)	6 (10.0)	1 (4.5)	2 (5.7)	2 (3.0)
Treatment-related TEAEs leading to treatment discontinuation	3 (13.0)	8 (18.2)	5 (8.3)	0 (0.0)	0 (0.0)	1 (1.5)
TEAEs known to be associated with pirfenidone						
GI disorder[b]	16 (69.6)	21 (47.7)	35 (58.3)	12 (54.5)	11 (31.4)	27 (40.3)
Photosensitivity[c]	2 (8.7)	5 (11.4)	3 (5.0)	1 (4.5)	0 (0.0)	1 (1.5)
Rash[d]	4 (17.4)	6 (13.6)	9 (15.0)	4 (18.2)	4 (11.4)	5 (7.5)
Dizziness	1 (4.3)	2 (4.5)	8 (13.3)	4 (18.2)	4 (11.4)	5 (7.5)

Table 3 continued

	Pirfenidone			Placebo		
	MMF (with or without corticosteroids) (*n* = 23)	Corticosteroids/ no MMF (*n* = 44)	No corticosteroids/ no MMF (*n* = 60)	MMF (with or without corticosteroids) (*n* = 22)	Corticosteroids/ no MMF (*n* = 35)	No corticosteroids/ no MMF (*n* = 67)
Weight decrease	4 (17.4)	4 (9.1)	3 (5.0)	1 (4.5)	2 (5.7)	3 (4.5)
Fatigue	3 (13.0)	6 (13.6)	12 (20.0)	2 (9.1)	5 (14.3)	12 (17.9)

Data are *n* (%)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GI* gastrointestinal, *MMF* mycophenolate mofetil, *PT* Medical Dictionary for Regulatory Activities Preferred Term, *SOC* system organ class, *TEAE* treatment-emergent adverse event, *ULN* upper limit of normal

[a]Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (ALT or AST $> 3 \times$ ULN + total bilirubin $> 2 \times$ ULN)

[b]SOC GI disorders

[c]PTs photodermatosis, photosensitivity reaction, pruritus, pruritus allergic, pruritus generalized

[d]PTs nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash follicular, exfoliative rash, solar dermatitis, solar urticarial, sunburn, erythema, dry skin

such, more research and accurate disease genotyping and phenotyping are required.

The SENSCIS study of nintedanib in systemic sclerosis-associated (SSc)-ILD suggested that MMF may have an additive effect in reducing FVC decline [11]; however, the present study indicated that pirfenidone may be less effective with concomitant MMF use. This may be because SENSCIS was in a patient population with SSc-ILD, since immunomodulators including MMF have been shown to benefit this population as a result of the autoimmune nature of the disease [20, 21]. However, uILD populations are more heterogeneous than those with a specific ILD diagnosis, such as SSc-ILD [4], so immunomodulators may not be consistently beneficial in this population. For example, it has been previously suggested that treatment with the immunomodulator cyclophosphamide may be beneficial for patients with IPAF but may be less effective in patients with non-IPAF uILD [8]. Moreover, the PANTHER-IPF trial showed that treatment with immunomodulators (a combination of prednisone, azathioprine, and *N*-acetylcysteine) was associated with detrimental outcomes including increased rate of death and hospitalization versus placebo in patients with IPF [22]. Considering that some patients with uILD have a similar disease course to IPF again suggests that immunomodulators may not benefit all patients with uILD. It is important to note that a greater proportion of patients (48.4%) in SENSCIS were receiving MMF compared with the present study (17.8%) and that previous corticosteroid use was not investigated in SENSCIS [11].

Unlike the present study, the INBUILD study reported that the introduction of immunomodulatory therapies, including MMF, during the study did not affect the benefit of nintedanib in patients with progressive fibrosing non-IPF ILD on reducing FVC decline versus placebo, although fewer patients were receiving MMF in INBUILD than in the present study (2.7% vs 17.8% [at randomization]) since this was a restricted therapy in INBUILD [12]. Moreover, INBUILD reported that the use of glucocorticoids at baseline (54.4% of patients) did not affect the benefit of nintedanib on reducing FVC decline versus placebo, although it should be noted that high-dose (greater than 20 mg/day) glucocorticoids were restricted [12]; similarly, the present study showed a beneficial treatment effect for pirfenidone on FVC change in patients not taking MMF regardless of previous corticosteroid use (31.2% of total patients). Likewise, the RELIEF trial showed that pirfenidone treatment was efficacious in patients with other non-IPF progressive fibrosing ILDs, the majority of whom were receiving immunomodulators at baseline (73% and 89% in the pirfenidone and placebo groups, respectively) [18].

The safety profile of pirfenidone versus placebo was generally similar between all the subgroups. The incidence of treatment-related TEAEs was higher in the MMF subgroup than the no-corticosteroids/no-MMF subgroup in pirfenidone-treated patients; this increase in treatment-related TEAEs appears to be driven by an increase in mild-to-moderate GI disorders in the MMF subgroup. The LOTUSS trial of pirfenidone in SSc-ILD also found that the safety profile of pirfenidone was comparable in the patients who did or did not take concomitant MMF; however, there was a lower proportion of patients reporting severe TEAEs or TEAEs leading to discontinuation in the MMF versus no-MMF subgroup [23], which was not the case in the current study.

Limitations of the present analyses include the low patient numbers, meaning that these data should be interpreted with caution and firm conclusions cannot be drawn. In addition, the analysis by corticosteroid use was a post hoc analysis (leading to subgroups of different sizes as a result of corticosteroid use not being a stratification factor, unlike the analysis by MMF use). The analysis by MMF use was restricted to use of MMF treatment at randomization, whereas the analysis by corticosteroid use included all patients who started corticosteroids prior to or at baseline. Therefore, it is unclear whether patients in the MMF or corticosteroid subgroups received these treatments throughout the study. Furthermore, no clinical information relating to the reasons for treating patients with MMF was available, but it is possible that the clinical features of patients who

received MMF were different to those who did not. Additionally, patients with uILD are a heterogeneous population [3]; some have a predominantly fibrotic phenotype like IPF whereas others have a predominantly inflammatory phenotype (including patients with IPAF) or a combination of both fibrotic and inflammatory phenotypes, which may mean that the effect of pirfenidone treatment varies on a case-by-case basis. It should be noted that the study included patients who did not have a biopsy, which is reflective of clinical reality where many patients will not or cannot have a biopsy. It is therefore possible that some of these patients may have had an underlying pathological pattern of usual interstitial pneumonia, which could have led to a diagnosis of IPF if they had a biopsy. Although, it is important to note that even patients with a low-confidence IPF diagnosis were excluded from the study. However, the exclusion of patients with a low-confidence IPF diagnosis, as well as patients who received corticosteroids after baseline, may have contributed to the small sample size, and the patients who were included in the current analyses may not be reflective of patients with uILD treated during real-world clinical practice. A further limitation of these analyses is that patients were not permitted to receive any other immunomodulators during the trial. Although MMF and corticosteroids are the common agents of choice, other immunomodulators may also be used to treat patients with uILD (e.g., cyclophosphamide); as such, further evaluation including a broader range of immunomodulators is required.

CONCLUSION

Although limited by design and small sample sizes, this subgroup analysis suggests that pirfenidone may be less effective in patients with uILD receiving MMF at randomization, whereas a beneficial treatment effect for pirfenidone on FVC change was observed in patients not receiving MMF at randomization regardless of previous corticosteroid use. Pirfenidone was well tolerated in patients with uILD regardless of MMF and/or corticosteroid use. Further research is needed to explore these findings in a larger group of patients in a study appropriately designed to determine the effects of concomitant immunomodulators with pirfenidone in patients with progressive fibrosing uILD.

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Compliance with Ethics Guidelines. 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.

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

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