Phase II Trial of Pirfenidone in Patients With Progressive Fibrosing Unclassifiable ILD (uILD)

RCT1880

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AIMS

- Interstitial lung diseases (ILDs) are heterogeneous and characterised by the development of pulmonary parenchyma abnormalities, including fibrosis[1]
- Accurate diagnosis of a specific ILD by a multidisciplinary team (MDT) aids disease management and prognosis[1,2]
- Some patients are diagnosed with unclassifiable ILD (uILD) as a result of[1–3]:
  - Non-specific or conflicting clinical, radiological or histopathological findings[3]
  - Inability or unwillingness of the patient to undergo certain diagnostic procedures[3]
- There are currently no approved treatments for patients with uILD[4]
- Two antifibrotic agents, pirfenidone and nintedanib, have been shown to slow disease progression in patients with idiopathic pulmonary fibrosis (IPF)[5–7]
  - Progressive fibrotic uILD is a form of ILD with mechanistic and clinical similarities to IPF[4,8]
- The objective of this randomised, controlled trial was to investigate the efficacy and safety of pirfenidone (2403 mg/day) vs. placebo over 24 weeks in patients diagnosed with progressive fibrotic uILD[4]

METHODS

Study Design

- This was a multicentre, international, double-blind, randomised, placebo-controlled Phase II trial (NCT03099187) that enrolled eligible patients aged 18–85 years with a confirmed MDT diagnosis of fibrosing uILD who met the following study inclusion criteria[4]:
  - Percent predicted forced vital capacity (%FVC) ⩾ 45%
  - Percent predicted carbon monoxide diffusing capacity (%DLco) ⩾ 30%
  - > 10% fibrosis on high-resolution computed tomography within the previous 12 months
  - Progressive disease within the previous 6 months, defined as either > 5% absolute decline in %FVC or significant symptomatic worsening not due to cardiac, pulmonary (worsening of underlying uILD was not included in this category), vascular or other causes, as determined by the investigator

Endpoints

- The primary objective of the study was to evaluate the efficacy of pirfenidone vs. placebo using change in FVC (mL) measured by daily home spirometry over 24 weeks
  - Patients performed a single spirometry reading using a portable handheld Micro spirometer (CareFusion, Kent, UK) at approximately the same time each day, and were blinded to their results
- Secondary and prespecified exploratory endpoints were also measured over 24 weeks and included:
  - Change in FVC (mL and %), %DLco and 6-minute walk distance (6MWD) at site visits
  - Change in University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) score, cough-visual analogue scale (VAS) score, Leicester Cough Questionnaire (LCQ) score and St. George's Respiratory Questionnaire (SGRQ) total score
  - Progression-free survival (PFS), defined as time to first occurrence of a > 10% absolute decline in %FVC, a > 50 m decline in 6MWD or death, or alternatively defined as time to first occurrence of a > 10% relative decline in %FVC, non-elective respiratory hospitalisation or death
- The nature and severity of treatment-emergent adverse events, withdrawals from treatment and study discontinuations were recorded

Statistical Analyses

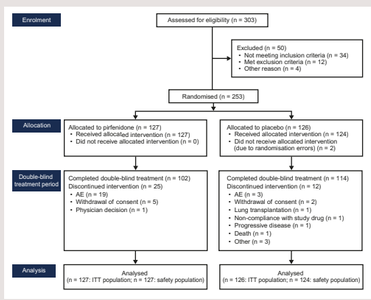
- For the primary endpoint, the planned analysis was to estimate daily FVC change for each patient using a linear regression model. This was extrapolated to predict change over 24 weeks, with comparison between treatment arms achieved using a t-test with a two-sided significance level of 5%
  - This model could not be applied because data were not normally distributed, therefore data are presented descriptively, with median selected as the most appropriate statistic, given the skewed nature of the data
  - No imputation was applied for missing data
- For the secondary and prespecified exploratory endpoints, all data were used without imputation, and *P*-values are reported descriptively without adjustment for multiplicity

RESULTS

Patient Population

- Between 15 May 2017 and 5 June 2018, 253 patients were randomised to receive either pirfenidone (n = 127) or placebo (n = 126) (**Figure 1**)
  - Baseline characteristics did not differ substantially between the treatment groups (**Table 1**)

Figure 1. Patient Enrolment and Outcomes



AE, adverse event; ITT, intent-to-treat.

Table 1. Demographic and Baseline Characteristics of Study Participants (ITT Population)

Characteristic*	Pirfenidone (n = 127)	Placebo (n = 126)
Age at screening, years	70.0 (61.0, 76.0)	69.0 (63.0, 74.0)
Male, n (%)	70 (55.1)	69 (54.8)
Historical surgical lung biopsy, n (%)	40 (31.5)	48 (38.1)
%FVC	71.0 (59.0, 87.3)	71.5 (58.0, 88.0)
%DLco	44.6 (36.9, 53.5)	48.0 (38.4, 59.0)
6MWD, m	372.0 (303.0, 487.0)	395.0 (325.0, 472.0)
Patients with a diagnosis of IPAF, n (%)	15 (11.8)	18 (14.3)
Patients taking concomitant MMF, n (%)	23 (18.1)	22 (17.5)
Dose intensity,† %	94.9 (78.5, 95.3)‡	95.3 (93.6, 95.5)‡

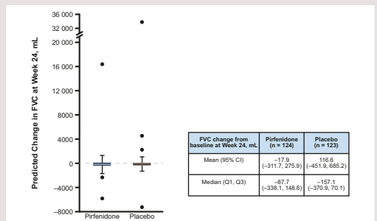
6MWD, 6-minute walk distance; %DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; IPAF, interstitial pneumonia with autoimmune features; ITT, intent-to-treat; MMF, mycophenolate mofetil; Q1, quartile 1; Q3, quartile 3.
* Data are presented as median (Q1; Q3) unless otherwise specified. † Dose intensity = (total dose received/total dose planned) x 100. ‡ n = 126. † n = 124.

- Overall, 251 patients received at least one dose of study drug (n = 127 pirfenidone; n = 124 placebo)
  - The median dose was 2281.62 mg/day for pirfenidone and 2299.80 mg/day for placebo

Primary Endpoint

- Analysis of the primary endpoint was impacted by high intra-individual variability in home spirometry values and issues applying linear regression to patients with a small number of readings collected in a short period of time
  - The data were not normally distributed; therefore, the planned statistical model could not be applied
- Median predicted change in FVC from baseline to Week 24 measured using home spirometry is presented in **Figure 2**

Figure 2. Boxplot of Median Predicted FVC Change (mL) From Baseline to Week 24 Measured Using Daily Home Spirometry (ITT Population)



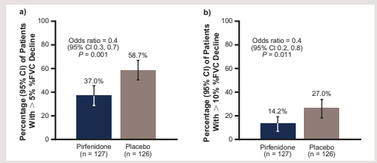
FVC change from baseline at Week 24, mL	Pirfenidone (n = 124)	Placebo (n = 123)
Mean (95% CI)	−17.0 (−311.7, 275.9)	116.6 (−451.9, 685.2)
Median (Q1, Q3)	−82.7 (−338.1, 148.6)	−157.1 (−370.9, 70.1)

CI, confidence interval; FVC, forced vital capacity; ITT, intent-to-treat; Q1, quartile 1; Q3, quartile 3.

Secondary and Exploratory Endpoints

- Change in FVC measured at site visits consistently favoured pirfenidone over placebo
  - Predicted mean (95% confidence interval) decline in FVC (mL) was lower in patients randomised to pirfenidone compared with placebo at Week 24:
    - Pirfenidone: −17.8 (−62.6, 27.0) mL
    - Placebo: −113.0 (−152.5, −73.6) mL
    - Pirfenidone vs. placebo: 95.3 (35.9, 154.6) mL; *P* = 0.002
  - Absolute declines of > 5% and > 10% in %FVC were reported less frequently in patients receiving pirfenidone vs. placebo (**Figure 3**)
  - A rank analysis of covariance (ANCOVA) model for %FVC for absolute change from baseline to last observed measurement yielded a *P*-value of 0.038
  - In subgroup analyses, a treatment benefit was generally observed regardless of age, gender, lung function and presence/absence of interstitial pneumonia with autoimmune features (**Figure 4**)
    - Subgroup analyses stratified by body weight and mycophenolate mofetil treatment appeared to suggest a differential treatment effect, but small sample sizes prevent meaningful interpretation of these data

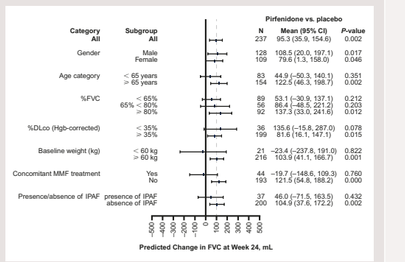
Figure 3. Percentage of Patients With Categorical Declines of (a) > 5% and (b) > 10% for %FVC (ITT Population)



CI, confidence interval; FVC, forced vital capacity; ITT, intent-to-treat.

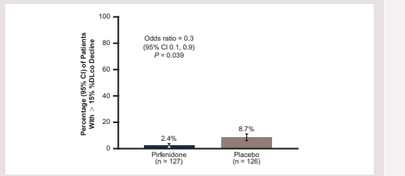
- Mean (standard deviation [SD]) change in %DLco from baseline to Week 24 was −0.7% (7.1) in the pirfenidone group (n = 97) and −2.5% (8.8) in the placebo group (n = 110)
- The percentage of patients experiencing a > 15% absolute decline in %DLco was lower in the pirfenidone group compared with the placebo group (**Figure 5**). However, rank ANCOVA results for change from baseline in %DLco did not favour pirfenidone (*P* = 0.087)

Figure 4. Subgroup Analysis of Mean Change in FVC From Baseline to Week 24 Measured Using Site Spirometry (ITT Population*)



CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; Hgb, haemoglobin; IPAF, interstitial pneumonia with autoimmune features; ITT, intent-to-treat; MMF, mycophenolate mofetil.
* Analysis excluded patients who did not reach Week 8 site spirometry.

Figure 5. Percentage of Patients With a Categorical Decline of > 15% for %DLco* (ITT Population)



CI, confidence interval; %DLco, percent predicted carbon monoxide diffusing capacity; ITT, intent-to-treat.
* Exploratory prespecified endpoint.

- Mean (SD) change in 6MWD from baseline to Week 24 was −2.0 (68.1) m in the pirfenidone group (n = 99) and −26.7 (79.3) m in the placebo group (n = 108)
- A > 50 m decline in 6MWD was reported in 28.3% and 27.8% of patients in the pirfenidone and placebo groups, respectively, with no demonstrated treatment benefit. However, rank ANCOVA results for change from baseline in 6MWD favoured pirfenidone (*P* = 0.040)
- Changes in UCSD SOBQ, cough-VAS, LCQ and SGRQ scores were similar between the pirfenidone and placebo groups (data not shown)
- Time-to-event analyses for PFS are shown in **Figure 6**

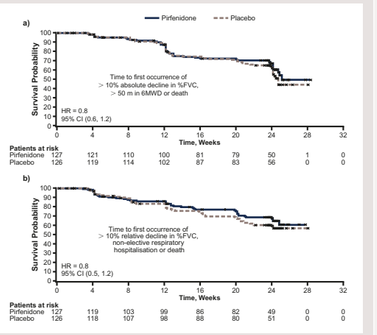
Safety

- Safety outcomes (**Table 2**) were consistent with the established safety profile of pirfenidone in patients with IPF, with no new safety signals identified[9]

Limitations

- Unanticipated technical and analytical issues with home spirometry prevented application of the planned statistical model to the primary endpoint data
- Patients with uILD comprise a heterogeneous population, therefore the effect of treatment may vary on a case-by-case basis
- The duration of treatment was short (24 weeks)

Figure 6. Time-to-Event Analyses, From Baseline, for PFS Defined as (a) > 10% Absolute Decline in %FVC, > 50 m Decline in 6MWD or Death, or Defined as (b) > 10% Relative Decline in %FVC, Non-Elective Respiratory Hospitalisation or Death (ITT Population)



6MWD, 6-minute walk distance; CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Table 2. Summary of TEAEs (Safety Population)

Event, n (%)	Pirfenidone (n = 127)	Placebo (n = 124)
Any TEAEs	120 (94.5)	101 (81.5)
Any treatment-related TEAEs	90 (70.9)	57 (46.0)
Any serious TEAEs*	18 (14.2)	20 (16.1)
Any severe TEAEs	29 (22.8)	28 (22.6)
Any treatment-related severe TEAEs	6 (4.7)	2 (1.6)
TEAEs of special interest†	0 (0.0)	0 (0.0)
TEAEs leading to death	1 (0.8)	1 (0.8)
Treatment-related TEAEs leading to death	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation	19 (15.0)	5 (4.0)
Treatment-related TEAEs leading to treatment discontinuation	16 (12.6)	1 (0.8)
Summary of treatment-related TEAEs known to be associated with pirfenidone		
GI disorder‡	60 (47.2)	32 (25.8)
Photosensitivity§	10 (7.9)	2 (1.6)
Rash‖	13 (10.2)	9 (7.3)
Dizziness	10 (7.9)	4 (3.2)
Weight decrease	10 (7.9)	1 (0.8)
Fatigue	16 (12.6)	12 (9.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; PT, Medical Dictionary for Regulatory Activities Preferred Term; SOC, System Organ Class; TEAEs, treatment-emergent adverse events; ULN, upper limit of normal.
* Only one TEAE in each treatment group was considered to be treatment-related. † 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 x ULN + total bilirubin >2 x ULN). ‡ SOC GI disorders. § PTs: photodermatosis, photosensitivity reaction, pruritus, pruritus allergic, pruritus generalised. ‖ PTs: nodular rash, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash follicular, exfoliative rash, solar dermatitis, solar urticarial, sunburn, erythema, dry skin.

CONCLUSIONS

- Results from this study support the conclusion that pirfenidone was effective in patients with progressive fibrotic uILD over 24 weeks, with an acceptable safety and tolerability profile
- Further clinical investigation of pirfenidone in patients with fibrosing uILD is supported
- The results of this study have important implications for future clinical trial design in patients with ILD; further analyses are required before daily home spirometry can be used as a primary outcome measure

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DISCLOSURES

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