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Original research

Inhaled pirfenidone solution (AP01) for IPF: a randomised, open-label, dose–response trial

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ABSTRACT

Introduction Oral pirfenidone reduces lung function decline and mortality in patients with idiopathic pulmonary fibrosis (IPF). Systemic exposure can have significant side effects, including nausea, rash, photosensitivity, weight loss and fatigue. Reduced doses may be suboptimal in slowing disease progression.

Methods This phase 1b, randomised, open-label, dose–response trial at 25 sites in six countries (Australian New Zealand Clinical Trials Registry (ANZCTR) registration number ACTRN12618001838202) assessed safety, tolerability and efficacy of inhaled pirfenidone (AP01) in IPF. Patients diagnosed within 5 years, with forced vital capacity (FVC) 40%–90% predicted, and intolerant, unwilling or ineligible for oral pirfenidone or nintedanib were randomly assigned 1:1 to nebulised AP01 50 mg once per day or 100 mg two times per day for up to 72 weeks.

Results We present results for week 24, the primary endpoint and week 48 for comparability with published trials of antifibrotics. Week 72 data will be reported as a separate analysis pooled with the ongoing open-label extension study. Ninety-one patients (50 mg once per day: n=46, 100 mg two times per day: n=45) were enrolled from May 2019 to April 2020. The most common treatment-related adverse events (frequency, % of patients) were all mild or moderate and included cough (14, 15.4%), rash (11, 12.1%), nausea (8, 8.8%), throat irritation (5, 5.5%), fatigue (4, 4.4%) and taste disorder, dizziness and dyspnoea (three each, 3.3%). Changes in FVC % predicted over 24 and 48 weeks, respectively, were −2.5 (95% CI −5.3 to 0.4, −88 mL) and −4.9 (−7.5 to −2.3,−188 mL) in the 50 mg once per day and 0.6 (−2.2 to 3.4, 10 mL) and −0.4 (−3.2 to 2.3, −34 mL) in the 100 mg two times per day group.

Discussion Side effects commonly associated with oral pirfenidone in other clinical trials were less frequent with AP01. Mean FVC % predicted remained stable in the 100 mg two times per day group. Further study of AP01 is warranted.

Trial registration number ACTRN12618001838202 Australian New Zealand Clinical Trials Registry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Though oral pirfenidone reduces lung function decline and mortality from idiopathic pulmonary fibrosis (IPF), systemic exposure runs the risk of substantial adverse effects.

WHAT THIS STUDY ADDS

⇒ ATLAS phase 1b trial finds inhaled pirfenidone (AP01) has fewer adverse effects than antifibrotics currently used to treat IPF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The potential for efficacy in slowing progression of fibrosis and ameliorating decline in forced vital capacity warrants further study.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a severe progressive lung disorder, leading to increasing breathlessness and cough with a profound impact on health-related quality of life. Many patients die of respiratory failure or comorbidities within 3–5 years of diagnosis.[1 2] IPF affects up to 200 000 Americans and 135 000 Europeans.[3 4] Worldwide, two oral antifibrotic medications are approved to treat IPF: nintedanib and pirfenidone.[5 6] At the recommended dosing, both can be associated with liver enzyme elevation and gastrointestinal side effects; oral pirfenidone is also associated with photosensitivity and rash.[7 8] In pooled oral pirfenidone trials (pirfenidone: n=1299; placebo: n=624), nausea (38% vs 16%), rash (25% vs 10%), dyspepsia (18% vs 7%), weight loss (16% vs 5%), vomiting (16% vs 6%) and liver enzyme elevation (3% vs 0.9%) were more common with oral pirfenidone than with placebo.[8] In pooled nintedanib trials (nintedanib: n=723; placebo: n=508), diarrhoea (62% v 18%), nausea (24% v 7%), abdominal pain (15% v 6%), liver enzyme elevation (14% v 3%), and vomiting (12% v 3%) were more common with nintedanib than with placebo.[7] These adverse events (AEs) may lead to dose reductions or discontinuations. In US and French studies of patients newly prescribed antifibrotics, more than 20% discontinued oral pirfenidone and 30% nintedanib after 6 months; 12-month discontinuation rates exceeded 40% for both antifibrotics.[9 10] Efficacy of both medications is suboptimal, slowing disease progression by ∼50% but not halting lung function decline.[5 6]

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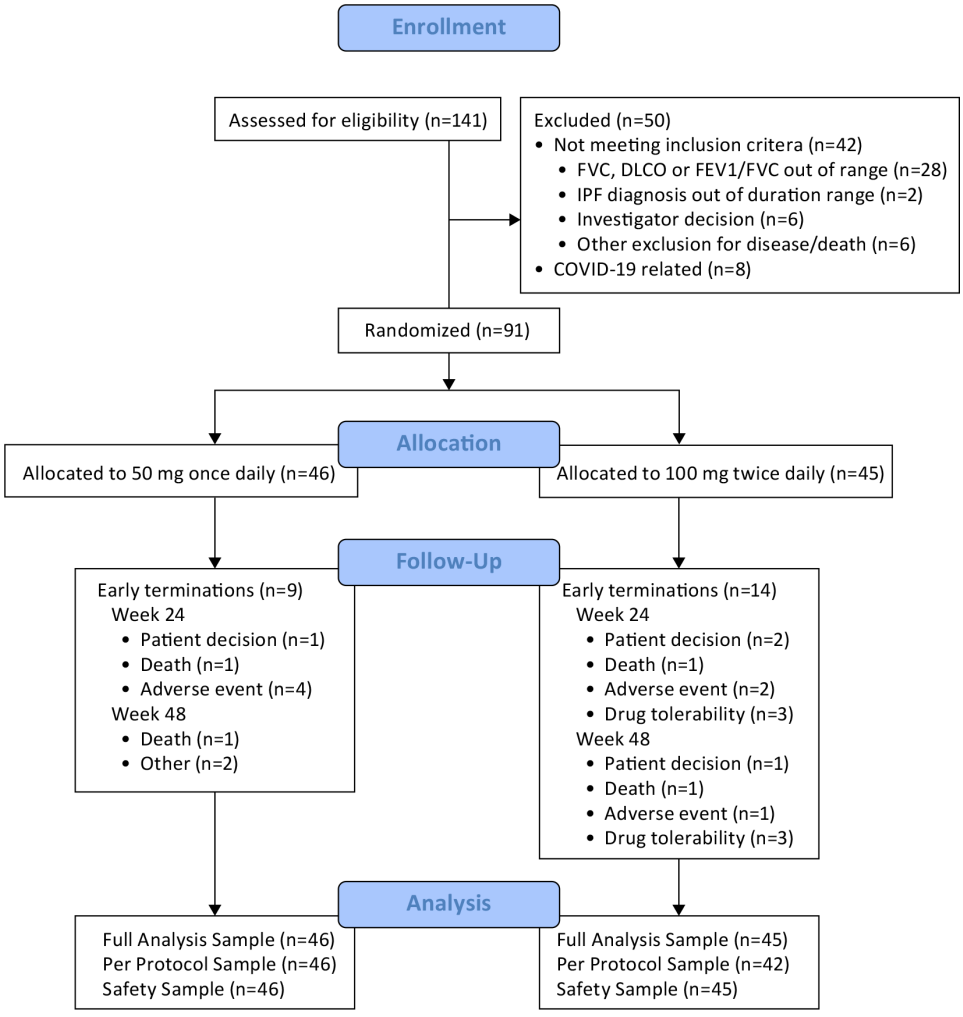


Figure 1 Study population to week 48. Based on a review of safety and efficacy performed after all patients completed 24 weeks, the Data and Safety Monitoring Board recommended all patients transition to the 100 mg twice-daily dose. A total of 31 patients transitioned from 50 mg once per day to 100 mg two times per day: 5 patients transitioned by 48 weeks, 16 more by 72 weeks and an additional 10 after 72 weeks. DLCO, diffusing capacity to carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Aerosol administration improves efficacy and safety of many drugs by increasing delivery to lung tissue and decreasing systemic exposure.[11] AP01 is an inhaled formulation of pirfenidone optimised for lung delivery. In a phase 1, single ascending dose study evaluating safety, tolerability and pharmacokinetics, the PARI investigational eFlow nebuliser delivered >40% of the dose to the lung and enabled alveolar delivery. AP01 was well tolerated by healthy volunteers and patients with IPF. Compared with the approved thrice-daily, 801 mg dose of oral pirfenidone, the highest dose of AP01 tested (100 mg) achieved 35-fold higher peak epithelial lining fluid concentrations with ~1/15 systemic exposure.[12]

The ATLAS study assessed the safety, tolerability and efficacy of two AP01 doses in patients with IPF. We present results for week 24, the primary endpoint and week 48 for comparability to published trials of antifibrotics. The Data and Safety Monitoring Board (DSMB) recommended transitioning all patients to the higher dose midstudy following review of week 24 data in all patients. Only five patients transitioned to the higher dose by the week 48 visit. An additional 16 patients on 50 mg once per day transitioned to 100 mg two times per day by week 72. Therefore, week 72 data will be reported as a separate analysis pooled with the ongoing open-label extension study.

METHODS

Study design

ATLAS is a 24-week (optional extension to 72 weeks) randomised, parallel-group, open-label trial conducted from May 2019 to October 2021 at 25 sites in Australia, New Zealand, Czech Republic, Poland, Netherlands and the UK. The trial was conducted in compliance with the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation and approved by local ethics committees. All patients provided written informed consent.

Eligibility

Principal eligibility criteria included being ≥40 years of age, with a confident diagnosis of IPF according to European Respiratory Society/American Thoracic Society (ERS/ATS) criteria within 5 years, forced vital capacity (FVC) ≥40% and ≤90% predicted and forced expiratory volume in 1 s (FEV_1)/FVC ratio ≥0.7, not currently taking oral pirfenidone or nintedanib. Exclusion criteria included acute IPF exacerbation requiring hospitalisation in the previous 3 months, any alternative diagnoses that could lead to pulmonary fibrosis or connective tissue disease,

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Table 1 Baseline patient characteristics

	50 mg once per day	100 mg two times per day	Total
Patients, n	46	45*	91
Asia-Pacific region, n (%)	21 (45.7)	21 (46.7)	42 (46.2)
Age at screening (years), mean (SD)	73.4 (7.0)	71.3 (8.1)	72.4 (7.6)
Male, n (%)	32 (69.6)	32 (71.1)	64 (70.3)
Former smoker, n (%)	33 (71.7)	32 (71.1)	65 (71.4)
FVC % predicted at screening, mean (SD)	71.4 (11.7)	72.4 (10.0)	71.9 (10.8)
DLCO % predicted at screening, mean (SD)	48.6 (14.0)	49.1 (10.7)	48.8 (12.4)
IPF duration in months at screening, median (range)	18.1 (2.4–60.4)	27.1 (0.6–58.3)	22.0 (0.6–60.4)
Diagnosis within 1 year, n (%)	10 (21.7)	14 (31.1)	24 (26.4)
CT pattern from scan, n (%)			
Typical UIP pattern	14 (30.4)	24 (53.3)	38 (41.8)
Probable UIP pattern	31 (67.4)	19 (42.2)	50 (54.9)
Indeterminate UIP pattern	1 (2.2)	2 (4.4)	3 (3.3)
QLFCAD mL, mean (SE), n	633.0 (297.1), 44	489.6 (292.3), 42	563.0 (301.8), 86
Prognostic biomarker above median, n (%)			
CXCL13	25 (54.4)	20 (45.5)	45 (50.0)
CCL18	22 (47.8)	23 (52.3)	45 (50.0)
MMP3	27 (58.7)	18 (40.9)	45 (50.0)

*Biomarker data were available for only 44 of the 45 patients in the 100 mg two times per day group.
CT, computed tomography; DLCO, diffusion capacity to carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; QLFCAD, quantitative lung fibrosis computer-aided diagnosis; SD, standard deviation; SE, standard error; UIP, usual interstitial pneumonia.

asthma, chronic obstructive pulmonary disease or active infection. Full eligibility criteria are provided in online supplemental table 1.

Randomisation and stratification

Patients were randomly assigned using interactive response technology 1:1 to AP01 50 mg once per day or 100 mg two times per day administered with a PARI investigational eFlow nebuliser. Randomisation was stratified by region (Asia-Pacific/Europe) and disease severity (FVC % predicted <50/≥50).

Sample size

The target sample size of 100 patients (50 per dose group) was selected to provide adequate data to assess the safety and tolerability of AP01 given once or two times per day and estimates of changes in outcomes over time. With the target sample size, there was a 92% chance of detecting an AE with a true population rate of 5%.

Study treatment

The first dose was administered at the study site. Patients experiencing cough limiting their ability to complete the first dose were pretreated with one to two puffs of salbutamol for remaining doses, as were patients with a history of asthma, smoking history ≥20 pack-years or ≥15% decrease in FEV_1 % predicted (post–pre dose) unless already receiving a long-acting beta-2 agonist.

Safety assessments

An independent DSMB reviewed safety data after the first 20 patients completed 4 weeks and when all patients completed 24 and 48 weeks. Safety outcome measures included treatment-emergent AEs, change in FEV_1 (post–pre dose) for the initial dose and changes in vital signs and clinical laboratory findings.

Efficacy assessments

Laboratory, in-clinic spirometry and patient-reported outcome (PRO) measures were collected every 4 weeks for 24 weeks, then every 12 weeks through week 72. Spirometry was performed according to ATS/ERS guidelines.[13] PROs included the Leicester Cough Questionnaire (LCQ) and the King's Brief Interstitial Lung Disease (KBILD) questionnaire.[14 15] Laboratory testing was performed using a central laboratory. Leicester Cough Monitor (LCM) 24-hour measurements were collected at baseline and weeks 12 and 24 and centrally scored.[16] High-resolution CT (HRCT) scans were performed at baseline and week 24 and centrally interpreted and quantified, including total lung capacity volume (litres) and quantitative lung fibrosis computer-aided diagnosis (QLFCAD) score (millilitres) for the whole lung.[17]

The primary efficacy endpoint was absolute change from baseline to week 24 in FVC % predicted. Prespecified secondary endpoints included change from baseline in diffusion capacity to carbon monoxide (DLCO), PROs, cough frequency and intensity, and extent of fibrosis and lung volumes measured by quantitative scoring of HRCT.

Analysis

All analyses were consistent with our prespecified Statistical Analysis Plan (provided in online supplemental materials). Safety, disposition and baseline analyses were conducted in patients who received ≥1 dose of AP01, and analyses for all other outcomes were performed on the per-protocol sample specified in the Statistical Analysis Plan. Inferential analyses implicitly handled missing data assuming missingness was explained by observed variables (missing at random). Change in FVC % predicted was analysed using a random coefficients model, with random slopes and intercepts for patients. Baseline FVC % predicted,[18] region, age at screening, sex, baseline DLCO % predicted[19] and baseline

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Table 2 Adverse events in 91 treated patients over 48 weeks

	50 mg once per day	100 mg two times per day	Total
Patients, n	46	45	91
AEs reported in ≥10% of patients in either dose group, n (%)*			
Cough	11 (23.9)	14 (31.1)	25 (27.5)
Rash†	6 (13.0)	8 (17.8)	14 (15.4)
Dyspnoea	6 (13.0)	7 (15.6)	13 (14.3)
Nausea	5 (10.9)	5 (11.1)	10 (11.0)
Idiopathic pulmonary fibrosis‡	6 (13.0)	3 (6.7)	9 (9.9)
Fatigue	3 (6.5)	5 (11.1)	8 (8.8)
Lower respiratory tract infection	2 (4.3)	6 (13.3)	8 (8.8)
Upper respiratory tract infection	1 (2.2)	7 (15.6)	8 (8.8)
SAEs, n (%)*			
Idiopathic pulmonary fibrosis‡	1 (2.2)	2 (4.4)	3 (3.3)
Dyspnoea	1 (2.2)	0	1 (1.1)
Haemoptysis	1 (2.2)	0	1 (1.1)
Cardiac failure	1 (2.2)	0	1 (1.1)
Pneumothorax	0	1 (2.2)	1 (1.1)
Pulmonary embolism	0	1 (2.2)	1 (1.1)
Pneumonia	1 (2.2)	1 (2.2)	2 (2.2)
Bacteraemia	1 (2.2)	0	1 (1.1)
Campylobacter infection	1 (2.2)	0	1 (1.1)
Cellulitis	1 (2.2)	0	1 (1.1)
Infectious pleural effusion	0	1 (2.2)	1 (1.1)
Lower respiratory tract infection	0	1 (2.2)	1 (1.1)
Lower respiratory tract infection viral	0	1 (2.2)	1 (1.1)
Parainfluenzae virus infection	0	1 (2.2)	1 (1.1)
Septic embolus	1 (2.2)	0	1 (1.1)
Lung adenocarcinoma stage I	0	1 (2.2)	1 (1.1)
Prostate cancer	0	1 (2.2)	1 (1.1)
Cerebral infarction	1 (2.2)	0	1 (1.1)
Embolic stroke	1 (2.2)	0	1 (1.1)
Chest discomfort	1 (2.2)	0	1 (1.1)
Musculoskeletal chest pain	1 (2.2)	0	1 (1.1)

*n (%) for AEs and SAEs are frequency (percentage) of patients with the event reported.
†Rash includes the following preferred terms: rash, rash macular, rash papular, rash erythematous and rash pruritic.
‡The idiopathic pulmonary fibrosis (IPF) preferred term includes progression, deterioration, exacerbation and worsening of IPF.
AEs, adverse events; SAEs, serious adverse events.

progression-related biomarkers (CXCL13, CCL18, MMP3, each categorised as >or ≤ median level) were included as covariates. The model required all covariates and three follow-up measurements of FVC % predicted for the intercept and slope to be identifiable. The average slope, representing FVC decline, was estimated for each dose group using the random coefficients model and compared between groups. Significance tests comparing dose groups were based on these fixed slope effects and summarised using p values and two-sided 95% CIs for the difference between dose groups. A similar analysis was conducted for FVC in litres. For patients who transitioned to 100 mg two times per day, spirometry data collected after transition were not included when estimating slopes. For visit-based analyses comparing means, a linear mixed-effects model was used with change from baseline in FVC as the dependent variable, patient as a random effect, fixed effect of time and time-varying effects for treatment group (dose group was treated as time-varying to accommodate patients who transitioned) and treatment-by-time interaction and baseline FVC % predicted, region, sex, baseline DLCO % predicted, age at screening, baseline progression-related biomarkers (CXCL13, CCL18, MMP3), each categorised as >median level versus ≤median level as fixed effects. To account for correlated repeated measures within patients, a spatial power variance–covariance matrix was used. These comparisons were summarised using least-squares means and two-sided 95% CIs.

Descriptive analyses were conducted for other endpoints. LCM data analyses include the subgroup with baseline cough frequency during awake hours ≥10 coughs/hour to assess treatment impact in patients for whom coughing is of the greatest concern.[20] The absolute change from baseline in fibrosis in the whole lung obtained from the HRCT scans was calculated and correlated with change from baseline in FVC (millilitres). PROs, including KBILD and LCQ, were summarised as absolute changes from baseline at each visit.

RESULTS

Patient information

Ninety-one patients enrolled (46 at 50 mg once per day, 45 at 100 mg two times per day); 77 (85%) of patients completed 24 weeks and 68 (75%) completed week 48 (figure 1). The target enrolment of 100 was not reached because the COVID-19 pandemic closed most sites from March to April 2020. Ongoing intermittent closures prevented some office visits and spirometry measurements.

All patients had a confident diagnosis of IPF, based on ATS guidelines (online supplemental table 1).[21] Although median IPF duration was shorter in the 50 mg once per day group, the percentage of patients diagnosed within 1 year was lower, and patients had higher quantitative fibrosis on average (table 1). A greater percentage of 50 mg once per day patients had CXCL13 and MMP3 above the median compared with 100 mg two times per day patients.

Safety

Initial doses were well tolerated with no adverse effects on respiratory rate, spirometry or oxygenation during or following administration; median administration times were 5 and 8 min for the 50 mg and 100 mg doses, respectively. Eight patients (9%) had cough associated with nebulisation. Of the eight, one patient received salbutamol before the first dose, four were given salbutamol to continue dosing and three did not require salbutamol. All cough events associated with first-dose nebulisation were mild or moderate in severity and transient.

AEs reported for ≥10% of patients included cough, rash, dyspnoea, nausea, IPF (includes progression, deterioration, exacerbation and worsening), fatigue, lower respiratory tract infection and upper respiratory tract infection (table 2). AEs generally occurred within 3 months, with median time to first AE being 53 (IQR 1–153) days for rash, 32 (9–187) days for nausea and 72 (22–155) days for fatigue. Cough (n=14/91, 15.4%) was the most reported treatment-related AE, with three events related to nebulisation (two in the 50 mg once per day group, one in the 100 mg two times per day group). Except for throat irritation, the incidences of the most common treatment-related AEs were

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Table 3 Pulmonary function test results for patients at baseline, 24 and 48 weeks

	50 mg once per day			100 mg two times per day		
		Change from baseline			Change from baseline	
	Baseline	24 weeks	48 weeks	Baseline	24 weeks	48 weeks
FVC % predicted						
Patients, n	46	26	28	42	26	28
Mean (SD)*	71.4 (11.8)	−1.7 (5.4)	−4.6 (5.6)	72.0 (9.6)	0.0 (7.0)	−0.4 (7.9)
Patients, n	–	35	39	–	34	34
Slope (95% CI)†	–	−2.5 (−5.3 to 0.4)	−4.9 (−7.5 to −2.3)	–	0.6 (−2.2 to 3.4)	−0.4 (−3.2 to 2.3)
Patients, n	–	26	28	–	26	28
LS mean (95% CI)‡	–	−1.0 (−3.2 to 1.2)	−3.5 (−5.7 to −1.3)	–	−0.7 (−3.0 to 1.6)	−2.8 (−5.1 to −0.6)
FVC						
Patients, n	46	26	28	42	26	28
Mean (SD)*	2.5 (0.6) L	−66 (191) mL	−191 (191) mL	2.6 (0.6) L	−17 (259) mL	−40 (286) mL
Patients, n	–	35	39	–	34	34
Slope (95% CI)†	–	−88 (−190 to 15)	−188 (−277 to −99)	–	10 (−91 to 110)	−34 (−127 to 60)
DLCO % predicted						
Patients, n	46	26	28	42	25	28
Mean (SD)*	47.7 (12.7)	−0.1 (4.3)	−3.3 (7.8)	49.1 (11.7)	0.2 (5.2)	−2.6 (6.9)
DLCO mL/min/mm Hg						
Patients, n	46	26	28	42	25	28
Mean (SD)*	10.0 (4.2)	−0.1 (0.9)	−0.7 (1.6)	10.4 (3.8)	0.1 (1.1)	−0.5 (1.4)

*Mean (SD) are calculated based on observed data with no imputation.
†Slope (95% CI) for FVC % predicted (or FVC mL) are from a random coefficients model with change from baseline in FVC % predicted (or FVC mL) as the dependent variable, patient and time (continuous) as random effects, fixed effect of time and treatment group and treatment-by-time interaction and baseline FVC % predicted, region, sex, baseline DLCO % predicted, age at screening, baseline progression-related biomarkers (CXCL13, CCL18, MMP3), each categorised as >median level versus ≤median level as fixed effects.
‡LS mean (95% CI) for FVC % predicted are from a random coefficients model with a spatial power variance–covariance matrix, change from baseline in FVC % predicted as the dependent variable, patient as a random effect, fixed effect of time and time-varying effects for treatment group and treatment-by-time interaction and baseline FVC % predicted, region, sex, baseline DLCO % predicted, age at screening, baseline progression-related biomarkers (CXCL13, CCL18, MMP3), each categorised as >median level versu ≤median level as fixed effects.
DLCO, diffusion capacity to carbon monoxide; FVC, forced vital capacity; LS, least squares.

lower for the 50 mg once per day group. One grade 3 event of parainfluenza virus infection was considered serious; all other treatment-related events were mild or moderate.

Thirteen serious AEs were reported in nine patients assigned 50 mg once per day, with 11 serious AEs in 7 patients assigned 100 mg two times per day (table 2). AEs leading to study termination were cough (n=2), progression of IPF (n=2), pneumonia (n=1), rash (as defined in table 2) (n=1) and abnormal CT chest scan (n=1), the latter in a patient suspected of having lung carcinoma who also had abnormal tumour markers at the time.

All liver AEs were mild or moderate and resolved. One patient in the 100 mg two times per day group had elevated hepatic enzymes considered related to treatment, which resolved after dose interruption. The patient was restarted on 50 mg once per day, rechallenged with 100 mg two times per day and hepatic enzyme levels remained within normal limits. All other events were judged unrelated to treatment and included two 50 mg once per day patients with elevated liver function tests, one 50 mg once per day patient with two increased blood bilirubin events, one 100 mg two times per day patient with increased blood potassium and one 100 mg two times per day patient with elevated serum creatinine.

There were four deaths among patients on study. There were two deaths (one in the 50 mg once per day group from embolic stroke/septic embolus and one in the 100 mg two times per day dose from IPF) among patients on study through 24 weeks and two additional deaths (one in the 50 mg once per day group from IPF, one in the 100 mg two times per day group from pulmonary embolism) between 24 and 48 weeks.

Efficacy

Baseline and changes from baseline in pulmonary function testing and sample sizes at landmark timepoints are shown in table 3 and figure 2. Mean changes from baseline in DLCO were comparable between dose groups.

The differences in slopes (100 mg two times a day − 50 mg once per day) were 3.0 (95% CI −0.9 to 7.0; p=0.133) at 24 weeks and 4.5 (95% CI 0.7 to 8.2; p=0.022) at 48 weeks.

The one-sided lower 95% CI limit for the difference with 50 mg once per day and 100 mg two times a day was −0.84 (n=35) and 2.0 (n=35) at 24 weeks and 0.19 (n=39) and 4.2 (n=35) at 48 weeks, respectively.

Change in the QLFCAD score correlated moderately well with change in FVC for 100 mg two times a day but did not correlate for 50 mg once per day (online supplemental figure 1). Three patients assigned 100 mg two times a day had markedly increased FVC at 24 weeks (380, 500 and 850 mL) and 48 weeks (600, 450 and 830 mL) and a corresponding reduction in QLFCAD score in the whole lung at 24 weeks (−237,–151 and −644 mL, respectively).

At baseline, 48% of patients (46% assigned to 50 mg once per day and 50% assigned to 100 mg two times a day) had cough frequency at baseline ≥10/hour while awake (figure 3).

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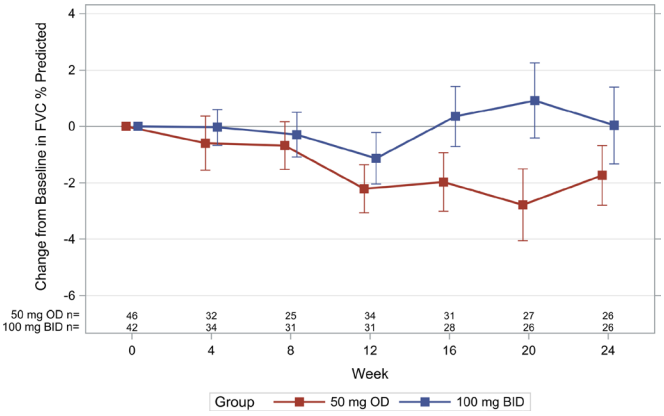


Figure 2 Change from baseline in FVC % predicted. Shown is the observed mean change from baseline in FVC % over 24 weeks. The error bars indicate the SE. BID, two times per day; FVC, forced vital capacity; OD, once per day.

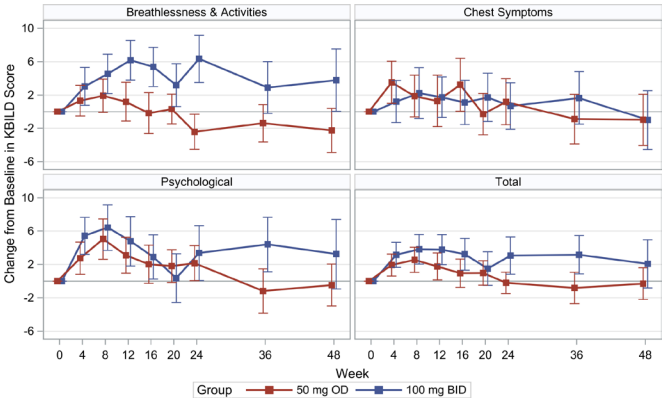


Figure 4 Change from baseline in KBILD scores. Shown is the observed mean change from baseline over 48 weeks in KBILD total and domain scores. The error bars indicate the SE. BID, two times a day; KBILD, King's Brief Interstitial Lung Disease questionnaire; OD, once per day.

Among patients with baseline cough ≥10 /hour, median cough frequency decreased in both dose groups; a more detailed analysis is presented in the online supplemental findings.

Regardless of baseline objective cough frequency, on average, patients reported modest changes in cough-related quality of life (online supplemental table 2). Similarly, small changes were observed in health-related quality of life within dose groups; however, differences in the breathlessness and activities, chest symptoms, psychological and total scores of the KBILD questionnaire were on average higher in the 100 mg two times a day group (online supplemental table 2; figure 4).

Transition to single dosing regimen

Based on a review of safety and efficacy performed after all patients reached the week 24 visit, the DSMB recommended transitioning all patients to 100 mg two times a day for the remainder of the trial because FVC data showed that most patients who received 100 mg two times a day were stabilised. Three patients transitioned to 100 mg two times a day before the week 48 visit and two patients at the week 48 visit. At 72 weeks, all patients had the option of continuing to receive 100 mg two times a day AP01 in an open-label extension trial; 47/54 patients (87%) chose to continue.

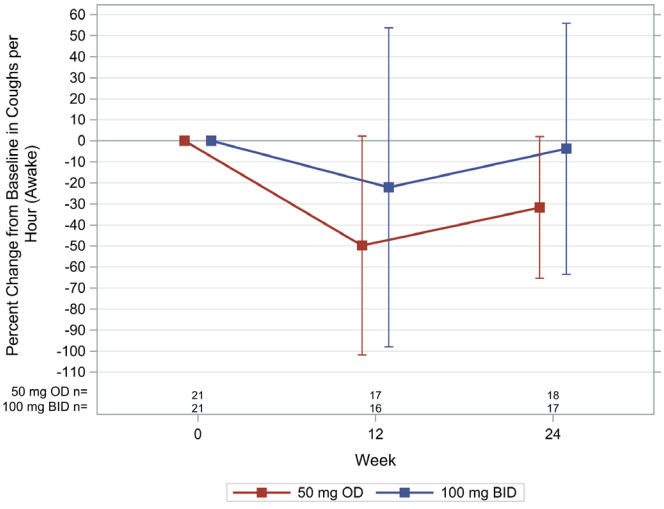


Figure 3 Per cent change from baseline in objective cough frequency measured by Leicester Cough Monitor. Shown is the observed median per cent change from baseline in objective cough frequency over 24 weeks for patients with baseline cough frequency ≥10 per hour. The error bars indicate the IQR. BID, two times a day; OD, once per day.

DISCUSSION

The ATLAS study shows the potential of aerosolised pirfenidone for improved safety and efficacy compared with oral pirfenidone in treating IPF. Both AP01 doses were well tolerated, and the most common dose-limiting AEs associated with oral pirfenidone[22] were reduced or absent. As with oral pirfenidone,[23] AEs generally occurred within 3 months. AEs deemed related to AP01 suggested a possible dose response for cough, rash, nausea, taste disorder, fatigue, dizziness and dyspnoea, with higher incidence in the 100 mg two times a day group than in the 50 mg once per day group.

The incidence of rash for 100 mg two times a day was 17.8%, and all events were mild or moderate. Rash events generally were managed by AP01 dose reduction, topical therapies or sun protection. Because patients intolerant to oral pirfenidone could be enrolled, these rash rates may over-represent expected incidence in the IPF and interstitial lung disease populations. Although patients with prior intolerance may be predisposed to sensitivity, not all patients with a history of rash on oral pirfenidone experienced rash with AP01. Patients with a history of intolerance to oral pirfenidone should not be assumed intolerant to AP01.

Taste disorder was reported in three patients assigned 100 mg two times a day, and dysgeusia was reported in one patient assigned 100 mg two times a day. Although the bitter taste of pirfenidone is masked by adding trace saccharin, sensitivity varied.

The low incidence of systemic AEs observed with AP01 is not surprising because the 100 mg two times a day nebulised dose leads to 1/15 systemic exposure of the approved oral pirfenidone daily dose and, regarding liver toxicity, has no first-pass effect. The elevated hepatic enzymes related to treatment in a single patient returned to normal limits after interruption and rechallenge. Early studies in small populations can miss rare AEs; however, the well-characterised safety profile of oral pirfenidone combined with decreased systemic exposure makes the detection of novel AEs outside the respiratory tract in larger studies unlikely.

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Cough is a common IPF symptom. Through 48 weeks, 25 patients were reported to have cough AE with cough AEs in 14 patients judged related to treatment. Most related events (n=12) were considered related to nebulisation and self-resolving or controllable by salbutamol or similar drugs or caused by another trigger such as upper respiratory tract infection and self-resolving. Two related cough events in the 100 mg two times a day group were considered long term. Two patients (one from each dose group) discontinued therapy due to cough. As with oral pirfenidone,[24] both doses of AP01 decreased frequency of cough in IPF patients with high baseline cough frequency, encouraging further study.

The 100 mg two times a day dose group showed significantly less loss of FVC % predicted compared with the 50 mg once per day group at 48 weeks. Changes in quantitative lung fibrosis scores from HRCT correlated well with changes in FVC for the 100 mg two times a day group. PRO results remained stable over 48 weeks in both dose groups with average changes from baseline in LCQ and KBILD domain and total scores less than the minimal clinically important difference.[20 25]

Three patients randomised to 100 mg two times a day had large increases in FVC at 24 and 48 weeks and steady improvement over the course of the study. At screening, their HRCT pattern was typical or probable UIP; time since diagnosis and disease severity varied, and these patients had no ongoing bronchodilator use, no signs of mucus plugging on screening HRCT and no productive cough. Structural changes seen with HRCT are eventually manifested as changes in FVC. FVC increases were consistent with improvements in quantitative fibrosis assessed by HRCT and similar improvements in other secondary efficacy endpoints, including KBILD scores.

The median administration time for the 100 mg two times a day dose was 8 min using the PARI investigational eFlow nebuliser. Duration is important because the pirfenidone half-life in epithelial lining fluid is ~10 min; efficacy due to a peak drug concentration would be decreased with extended nebulisation.[26] Nebulisers with lower delivery efficiency, slower administration or larger particle sizes favouring airway delivery would likely not deliver AP01 with optimal efficacy and safety. Our study design does not lend itself to clearly determining whether the difference seen in efficacy between the 50 and 100 mg doses at 48 weeks resulted from the dose amount or dose frequency.

Findings of this phase 1b study, designed to establish multi-dose safety and tolerability and to obtain variability and effect size estimates, should be interpreted cautiously. Blinding dose groups was not feasible because it would require a diluted formulation to produce equal volumes, leading to reduced C_{max} levels with the 50 mg dose. A placebo-control group without the allowance of background therapies was not included because approved antifibrotic therapies are available for the target IPF population. Spirometry data were missing from some post-baseline visits because of site restrictions due to the COVID-19 pandemic and early terminations. A slope-based analysis was used to leverage all observed data in estimating change over time in FVC % predicted, and a visit-based analysis showed consistent findings at weeks 24 and 48.

In summary, inhaled pirfenidone (AP01) is a promising treatment for IPF. Future studies exploring the potential for fewer adverse effects and improved efficacy compared with current antifibrotics in reducing or slowing progression of fibrosis, ameliorating decline in FVC and meaningfully improving quality of life are warranted.

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REFERENCES

1 Kreuter M, Swigris J, Pittrow D, *et al*. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. *Respir Res* 2017;18:139.
2 Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet* 2017;389:1941–52.
3 American thoracic society. idiopathic pulmonary fibrosis: diagnosis and treatment. international consensus statement. american thoracic society (ats), and the european respiratory society (ERS). *Am J Respir Crit Care Med* 2000;161:646–64.
4 Raghu G, Chen S-Y, Yeh W-S, *et al*. Idiopathic pulmonary fibrosis in US medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med* 2014;2:566–72.
5 Richeldi L, du Bois RM, Raghu G, *et al*. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
6 Noble PW, Albera C, Bradford WZ, *et al*. Pirfenidone in patients with idiopathic pulmonary fibrosis (capacity): two randomised trials. *Lancet* 2011;377:1760–9.
7 Boehringer Ingelheim Pharmaceuticals. OFEV® (nintedanib) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals,
8 Lancaster L, Albera C, Bradford WZ, *et al*. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir Res* 2016;3:e000105.
9 Lalla D, Bengston L, Raimundo K, *et al*. Pirfenidone and nintedanib compliance and persistence in A real world setting. *Am J Respir Crit Care Med* 2017;195:A5351.
10 Belhassen M, Dalon F, Nolin M, *et al*. Comparative outcomes in patients receiving pirfenidone or nintedanib for idiopathic pulmonary fibrosis. *Respir Res* 2021;22:135.
11 Clarke SW, Newman SP. Therapeutic aerosols 2 -- drugs available by the inhaled route. *Thorax* 1984;39:1–7.
12 Khoo JK, Montgomery AB, Otto KL, *et al*. A randomized, double-blinded, placebo-controlled, dose-escalation phase 1 study of aerosolized pirfenidone delivered via the PARI investigational eflow nebulizer in volunteers and patients with idiopathic pulmonary fibrosis. *J Aerosol Med Pulm Drug Deliv* 2020;33:15–20.
13 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
14 Birring SS, Prudon B, Carr AJ, *et al*. Development of a symptom specific health status measure for patients with chronic cough: Leicester cough questionnaire (LCQ). *Thorax* 2003;58:339–43.
15 Patel AS, Siegert RJ, Brignall K, *et al*. The development and validation of the King's brief interstitial lung disease (K-BILD) health status questionnaire. *Thorax* 2012;67:804–10.
16 Birring SS, Fleming T, Matos S, *et al*. The Leicester cough monitor: preliminary validation of an automated cough detection system in chronic cough. *Eur Respir J* 2008;31:1013–8.
17 Kim HG, Tashkin DP, Clements PJ, *et al*. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. *Clin Exp Rheumatol* 2010;28:S26–35.
18 Quanjer PH, Stanojevic S, Cole TJ, *et al*. Multi-Ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
19 Stanojevic S, Graham B, Cooper B, *et al*. Official ERS technical standards: global lung function initiative reference values for the carbon monoxide transfer factor for caucasians. *Eur Respir J* 2020;56.
20 Birring S, Muccino D, Bacci ED, *et al*. Defining minimal clinically important differences (MCID) on the Leicester cough questionnaire (LCQ): analyses of a phase 2 randomized controlled trial in chronic cough. *Journal of Allergy and Clinical Immunology* 2019;143:AB52.
21 Raghu G, Remy-Jardin M, Myers JL, *et al*. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–68.
22 Genentech USA Inc. Prescribing information for ESBRIET® (pirfenidone) capsules and film-coated tablets, for oral use. 2016. Available: https://www.gene.com/download/pdf/esbriet_prescribing.pdf
23 Lancaster LH, de Andrade JA, Zibrak JD, *et al*. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2017;26:170057.
24 van Manen MJG, Birring SS, Vancheri C, *et al*. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2017;50:1701157.
25 Sinha A, Patel AS, Siegert RJ, *et al*. The King's brief interstitial lung disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ Open Respir Res* 2019;6:e000363.
26 Kaminskas LM, Landersdorfer CB, Bischof RJ, *et al*. Aerosol pirfenidone pharmacokinetics after inhaled delivery in sheep: a viable approach to treating idiopathic pulmonary fibrosis. *Pharm Res* 2019;37:3.

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