BMC Pulmonary Medicine

RESEARCH

Open Access

Improved quality of life, reduced quantitative lung fibrosis in a trial of inhaled pirfenidone for idiopathic pulmonary fibrosis

Grace Hyun J. Kim[1], Felix A. Woodhead[2], Deepthi Nair[2], Hao Bao[2], Howard M. Lazarus[2], Craig S. Conoscenti[2] and Jonathan G. Goldin[1,3*]

Abstract

Background AP01, a novel formulation of inhaled pirfenidone, has demonstrated potential for improved efficacy and safety for idiopathic pulmonary fibrosis (IPF) vs. oral pirfenidone. A 72-week phase 1b study, ATLAS, suggested reliable correlations between structural changes revealed by high-resolution computed tomography (HRCT) and functional changes in forced vital capacity (FVC). Correlations between symptom improvement and structural changes are less established. Using ATLAS data, this study aims to investigate correlations between quantitative HRCT scores and changes in patient-reported outcomes (PROs) in AP01-treated patients with IPF.

Methods Patients ($N=91$) received AP01 50 mg qd or 100 mg bid. FVC, quantitative lung fibrosis (QLF), and PRO measures including King's Brief Interstitial Lung Disease questionnaire (KBILD) assessed functional, structural, and symptomatic changes over 48 weeks. Non-contrast HRCTs were performed at baseline and 24 weeks; improvement was defined as > 2% decrease in QLF score.

Results Among 69 patients with sufficient quality HRCT scans, similar proportions on both regimens exhibited QLF improvement (50 mg qd: 16%; 100 mg bid:16%) and QLF stabilisation ($-2\% \leq \Delta QLF \leq 2\%$) (50 mg qd: 47%; 100 mg bid: 55%). 100-mg bid subjects with improved QLF exhibited increased mean KBILD total scores from baseline beginning week 8 (8 points) through week 48 (> 20 points) (minimal clinically important difference = 5 points).

Conclusions A strong and lasting association between structural and symptomatic improvements confirms functional changes with AP01 and supports evaluation of the 100_mg bid dose.

Clinical trial registration AustralianNew Zealand Clinical Trials Registry Identifier ACTRN 12,618,001,838,202 URL: https://www.anzctr.org.au the trial registration took place before the first patient enrolled trial registration was 12 November 2018 and first patient enrolled on 06 January 2019.

Keywords Idiopathic pulmonary fibrosis, Interstitial lung disease, Lung function, Quality of life, HRCT, KBILD, Minimal clinically important difference, Inhaled pirfenidone

*Correspondence:
Jonathan G. Goldin
JGoldin@mednet.ucla.edu
[1]Department of Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[2]Avalyn Pharma Inc., Boston, MA, USA
[3]Voiant, Los Angeles, CA, USA

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

Background

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease occurring primarily in older adults, characterised by a chronic course and a generally poor prognosis. It is a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the pathological pattern of usual interstitial pneumonia (UIP). IPF follows a variable clinical course in which periods of relative stability are mixed with episodes of accelerated decline, with a median survival of 3 to 5 years [1]. IPF can be treated with either pirfenidone or nintedanib, which have been shown to decrease the rate of forced vital capacity (FVC) decline in IPF patients compared with placebo [2]. However, both oral pirfenidone and nintedanib have challenging side effects that can limit their use. Therefore, new, better-tolerated therapies with comparable or improved efficacy continue to be needed in this patient population.

Inhalation therapy holds promise as a possible treatment for IPF. In general, inhaled formulations improve safety and efficacy by reducing systemic exposure and improving delivery to the lung tissue [3]. AP01 is a novel form of pirfenidone optimised for delivery by inhalation through a specially designed PARI investigational eFlow nebuliser (eFlow). AP01 phase 1 data showed that 100 mg of nebulised AP01 achieved a peak alveolar concentration 35 times that reached with the licensed oral dose of pirfenidone (801 mg three times daily), with ~ 1/15 the plasma level [4]. AP01 was well tolerated by normal healthy volunteers and IPF patients.

Safety and therapeutic effect of AP01 in the IPF population were assessed in ATLAS, a phase 1b, randomised, open-label, dose-response study. Patients were randomised at 25 sites to receive one of two doses of AP01, 50 mg once daily (qd) or 100 mg twice a day (bid) [5]. Both doses were well tolerated, and side effects associated with oral pirfenidone were notably less frequent, consistent with the reduced systemic exposure. The primary efficacy endpoint, change from baseline in FVC % predicted, remained stable in the 100-mg bid group. Further, symptoms as assessed by patient-reported outcomes (PROs), including the King's Brief Interstitial Lung Disease (KBILD) questionnaire and the Leicester Cough Questionnaire (LCQ), remained stable or showed improvement. Change from baseline in FVC correlated with quantitative computed tomography (QCT) measures of lung fibrosis in patients receiving 100 mg bid AP01 [6].

Quantitative CT offers the potential to measure disease extent and change over time, which may be useful as a prognostic and outcome biomarker [7–9]. Several phase 2 and phase 3 clinical studies have explored using QCT measures of lung fibrosis [10–12]. FVC, a measure of function, is the most widely accepted primary endpoint for IPF trials. FVC and QCT, a measure of structure, have been shown to correlate in several studies, including ATLAS. Beyond function and structure, patients, clinicians, and regulators have called for the consideration of additional endpoints that better reflect patient experience, including multifactorial endpoints based on how the patient "feels, functions or survives," together with more accessible PROs [6, 7].

Here, we report detailed quantitative high-resolution computed tomography (HRCT) results from the 72-week ATLAS trial with AP01 50 mg qd or 100 mg bid, as well as post-hoc analyses investigating the correlation of structure and symptom improvements as a measure of patient experience in IPF.

Methods

Study design and population

The phase 1b, randomised, open-label, dose-response, multicenter ATLAS study was conducted at 25 sites in six countries from May 2019 to October 2021 (ANZCTR: ACTRN 12618001838202) [5]. Patients were randomised in a 1:1 ratio to receive either AP01 50 mg qd or 100 mg bid (for 24 weeks, with a possible extension to 72 weeks). AP01 was administered with an investigational eFlow® nebuliser system (PARI Pharma GmbH). The CONSORT flow diagram of this study is presented in Fig. 1.

This study was conducted in compliance with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Council for Harmonisation. Local ethics committees/institutional review boards approved the protocol for each site, and all patients provided written informed consent before enrolment. Safety results were reviewed by a Data and Safety Monitoring Board.

Eligible patients were adults aged 40 years or older diagnosed with IPF within 5 years meeting the following criteria: 1) FVC 40%-90% predicted measured by spirometry; and 2) intolerant of, unwilling to take, or ineligible for oral pirfenidone or nintedanib; complete inclusion/exclusion criteria published previously [5].

The diagnosis of IPF was defined in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) clinical practice guideline [1]. Per ATS/ERS guidance, an available HRCT chest scan, obtained from the patient's provider within the past 12 months or performed during screening, or a surgical lung biopsy was evaluated by site investigators. The HRCT scans were reviewed at sites to confirm the diagnosis of IPF by demonstrating the presence of definite or probable UIP pattern. The previously published quantitative lung fibrosis (QLF) algorithm was used to quantitate the extent of pulmonary fibrosis [13].

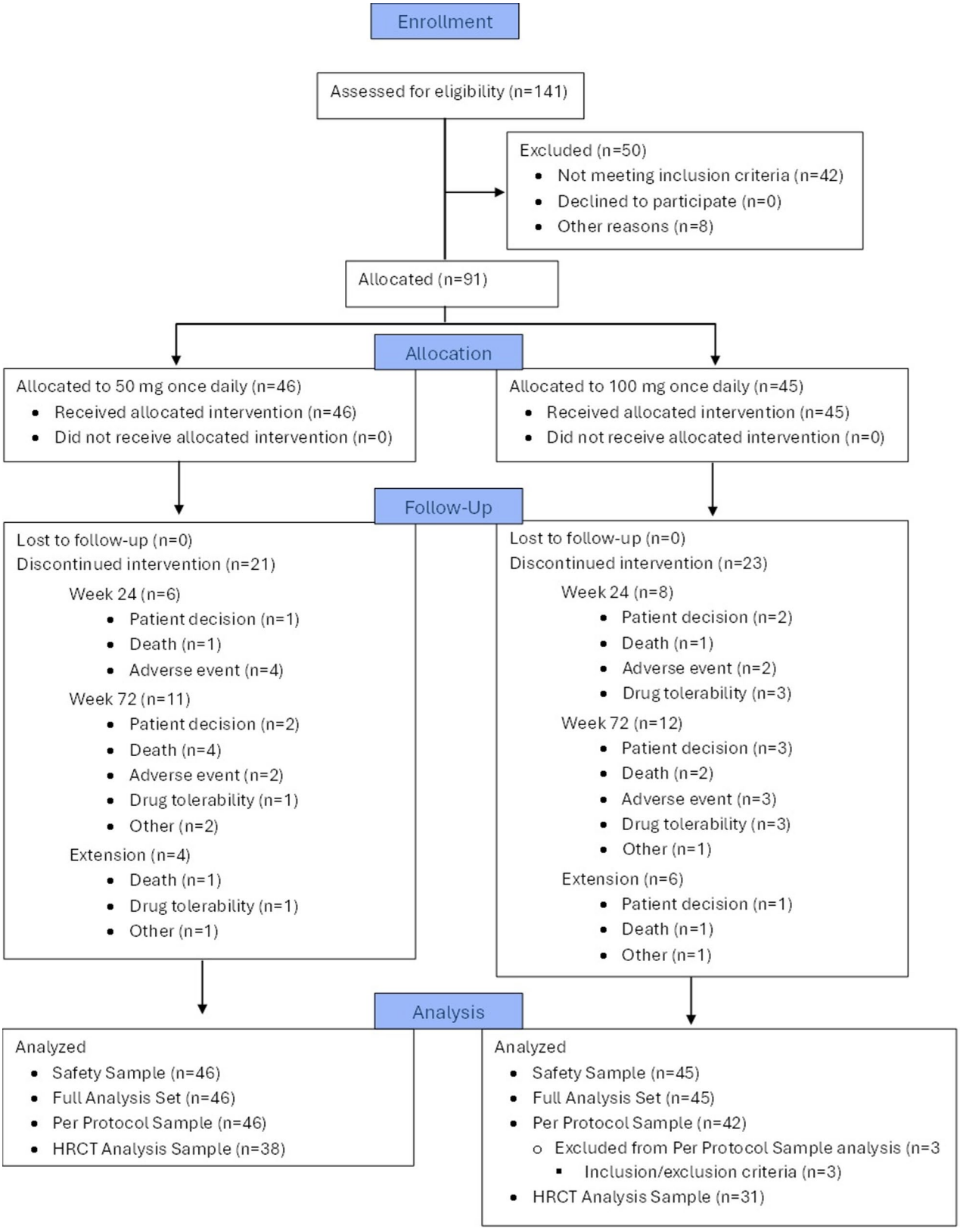


Fig. 1 CONSORT flowchart for the ATLAS study

Outcomes and data collection

Efficacy outcome measures in ATLAS included the absolute change in FVC % predicted (primary endpoint) and PRO scores from baseline to week 24 [5]. Prespecified secondary efficacy endpoints included the change from baseline in extent of fibrosis and lung volumes as measured by HRCT. Prespecified exploratory outcomes included correlation of the extent of fibrosis and lung volumes, as measured by HRCT at baseline and 24 weeks with spirometry.

Thin section non-contrast volumetric chest HRCT scans were performed at baseline on all subjects unless they had had an acceptable scan within the preceding month. A follow-up CT was originally scheduled at 24 weeks, but because of coronavirus disease 2019 (COVID-19) pandemic restrictions, this scan could be rescheduled for the next visit at 36 weeks. All follow-up HRCT scans are referred to hereafter as the 24-week scan. The QLF computer-aided score was expressed both as a percentage of pixels and in milliliters (mL) for the whole lung and each lobe, and the total lung capacity (TLC) volume in liters (L). The extent can be expressed in two scales of the percentage of involvement (%) or volume (mL) by multiplying the extent of disease in the percent scale and lung volume from HRCT [13, 14]. All HRCT personnel were blinded to treatment assignment.

PRO scores included the KBILD questionnaire, which was collected every four weeks for 24 weeks, then every 12 weeks through week 72 [5, 15, 16]. The KBILD questionnaire is validated for use in ILD patients [16]. It comprises questions relating to "breathlessness and activities," chest symptoms, and psychological factors; each of these domains, as well as the total, has a scoring range of 0 to 100, with 100 being the best health status. The minimally clinically important difference (MCID) in total KBILD has been reported to be 5 points [17].

Statistical analysis

Sample size calculations have been published previously [5].

For the analyses reported here, demographic and disease characteristics at baseline were summarised by dose group for patients with both a baseline and 24-week scan. QLF, quantitative ground glass (QGG), quantitative honeycomb (QHC), and TLC at baseline and 24 weeks, as well as absolute change from baseline to 24 weeks, were calculated and summarised descriptively by dose group.

A linear model was used to examine differences between dose groups in the change from baseline in whole-lung QLF from baseline to 24 weeks. Change from baseline was the dependent variable, and the dose group was the predictor variable. Baseline whole-lung QLF, geographic region, age at screening, sex, baseline diffusing capacity to carbon monoxide % predicted, and baseline progression-related biomarker values (CXCL13, CCL18, and MMP3, each categorised as > median level vs. ≤ median level), as well as time of the HRCT scan (relative to baseline in weeks), were considered for adjustment as covariates. Disease progression was categorised by change from baseline in QLF as a pre-defined percentage of the whole lung (improved: < -2%; stable: ≥ -2% and ≤ 2%, worsened: > 2%) [12]. Mean changes from baseline in KBILD total and domain scores were summarised and plotted over time by QLF progression category for each dose group to examine the relationship between quality of life (QOL) and disease progression. Missing data were not imputed. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., USA).

Results

All 91 patients randomised had a baseline HRCT scan collected, and 94.5% (86/91) passed image quality review for quantitative imaging analyses. At 24 weeks, 77 patients had follow-up. A 24-week HRCT scan was collected for 91% (70/77) patients, of which 98.6% (69/70) were performed per protocol. Thus, 69 patients had both a baseline and 24-week HRCT scan available (i.e., patients with paired HRCT scans) for analysis, including 38 patients in the 50-mg qd group and 31 in the 100-mg bid group. In these 69 patients, 47 HRCT scans were performed at 24 weeks, 19 were delayed until 36 weeks because of COVID-19 restrictions, and 3 were performed early (12, 16, and 20 weeks) because of termination from the study. The results of analyses conducted in these 69 patients with paired HRCT scans are reported here.

Demographics and baseline characteristics were similarly distributed in both dose groups, except HRCT pattern and QLF at baseline (Table 1). The 50-mg qd group had a smaller percentage of patients with a typical UIP pattern and greater fibrosis, both in mL and as a percentage of the whole lung, compared with the 100-mg bid group.

Structural changes (via HRCT parameters)

Table 2 displays descriptive summaries of absolute and % changes from baseline at 24 weeks in whole-lung HRCT parameters by dose group. The mean change from baseline in QLF showed a larger increase (i.e., less disease stabilisation) in the 50-mg qd group than in the 100-mg bid group. Analyses of the change in TLC were consistent with these results, showing a larger decrease in the 50-mg qd group. The adjusted, least-squares mean change from baseline in QLF was +25.7 mL in the 50-mg qd dose group and −29.5 mL in the 100-mg bid dose group, with a difference (100 mg bid − 50 mg qd) of -55.2 mL (95% CI: -145.6 to 35.2 mL). On average, there appears to be a smaller increase in QLF and a larger reduction in QGG

Table 1 Characteristics of patients with baseline and a 24-week HRCT scans by dose group

Characteristic	50 mg qd (*N* = 38)	100 mg bid (*N* = 31)	Total (*N* = 69)
Region, n (%)			
Asia Pacific	20 (52.6)	16 (51.6)	36 (52.2)
Europe	18 (47.4)	15 (48.4)	33 (47.8)
Age at screening (years), mean (SD)	73.4 (70.0)	70.7 (8.5)	72.2 (7.8)
Male, n (%)	28 (73.7)	24 (77.4)	52 (75.4)
White Race, n (%)	37 (97.4)	29 (93.5)	66 (95.7)
Former smoker, n (%)	27 (71.1)	22 (71.0)	49 (71.0)
Spirometry			
FVC % predicted at screening ≥ 50% predicted, n (%)	35 (92.1)	31 (100.0)	66 (95.7)
FVC at baseline, mean (SD)			
L	2.5 (0.59)	2.7 (0.64)	2.6 (0.62)
% predicted	69.8 (12.04)	73.2 (9.03)	71.3 (10.85)
FEV_1% predicted at baseline, mean (SD)	76.2 (12.65)	77.4 (9.80)	76.8 (11.39)
D_{LCO} % predicted at baseline (mL/min/mm Hg), mean (SD)	47.2 (13.36)	48.3 (11.01)	47.7 (12.28)
HRCT			
Pattern, n (%)			
Typical UIP	14 (36.8)	17 (54.8)	31 (44.9)
Probable UIP	23 (60.5)	12 (38.7)	35 (50.7)
Indeterminate UIP	1 (2.6)	2 (6.5)	3 (4.3)
QLF at baseline, mean (SD)			
mL of whole lung	645.6 (307.52)	478.7 (304.25)	570.6 (315.10)
% of whole lung	18.4 (11.02)	11.9 (7.89)	15.5 (10.21)
Ground glass at baseline, mean (SD)			
mL of whole lung	729.9 (311.68)	727.6 (258.60)	728.8 (286.99)
% of whole lung	19.2 (6.53)	17.7 (6.10)	18.6 (6.34)
Honeycomb at baseline, mean (SD)			
mL of whole lung	22.7 (31.16)	20.2 (21.94)	21.6 (27.24)
% of whole lung	0.6 (0.89)	0.5 (0.56)	0.6 (0.76)
Total lung capacity (L), mean (SD)	3.8 (0.90)	4.2 (0.89)	4 (0.91)
KBILD score at baseline, mean (SD)			
Total	53.8 (13.54)	56.5 (11.82)	55.0 (12.78)
Breathlessness and activities	40.6 (16.97)	43.0 (19.94)	41.7 (18.27)
Chest symptoms	64.7 (23.73)	69.8 (21.57)	67.0 (22.76)
Psychological	53.8 (18.50)	57.7 (15.93)	55.6 (17.37)

All 24-week HRCT scan statistics included patients with an HCRT scan performed at 24 weeks, at 36 weeks (a rescheduled 24-week visit because of the coronavirus disease 2019 pandemic), or during the End of Treatment visit

bid Twice a day, D_{LCO}Diffusing capacity to carbon monoxide, FEV_1Forced expiratory volume in 1 s, *FVC* Forced vital capacity, *HRCT* High-resolution computed tomography, *KBILD* King's Brief Interstitial Lung Disease questionnaire, *qd* Once daily, *QLF* Quantitative lung fibrosis, *UIP* Usual interstitial pneumonia

in the 100-mg bid group than in the 50-mg qd group, whereas the latter showed better stability on QHC.

The quantitative evaluation of HRCT for a representative individual patient in the 100-mg bid dose group is shown in Fig. 2, with the basis for QLF and QGG indicated by blue and yellow dots, respectively. This patient's QLF score improved by 151 mL from a baseline value of 600 mL (15.2%) to 449 mL (11.0%), and the QGG score improved by 250 mL from a baseline value of 1022 mL (25.9%) to 772 mL (18.9%). TLC increased correspondingly from 3.95 L at baseline to 4.09 L at 24 weeks.

Individual changes from baseline in QLF (%) at 24 weeks are illustrated in Fig. 3. The proportion of patients who improved (ΔQLF < -2%) was similar (16%) in both dose groups. Stabilisation (-2% ≤ ΔQLF ≤ 2%) was achieved in a larger percentage of patients in the 100-mg bid group. Overall, 22 (71%) patients improved or stabilised in the 100-mg bid group vs. 24 (63%) in the 50-mg qd group.

Correlations: structure / symptom improvements

Cross-classification of patients by symptom improvement, assessed by KBILD, and fibrosis improvement, assessed by QLF, shows the extent of agreement of these measures. Table 3 presents categorical summaries of KBILD improvement, with improvement defined as change from baseline ≥ MCID, and by QLF improvement

Table 2 Absolute and change from baseline in whole-lung HRCT parameters by dose group

Parameter, mean (SD)	50 mg qd (*N* = 38)	100 mg bid (*N* = 31)	Total (*N* = 69)
QLF			
mL			
Week 24	665.9 (331.29)	483.3 (317.36)	583.9 (335.45)
Change from baseline	20.3 (171.24)	4.6 (160.58)	13.3 (165.51)
%			
Week 24	19.3 (11.69)	12.4 (9.23)	16.2 (11.14)
Change from baseline	1.0 (6.15)	0.5 (4.55)	0.7 (5.46)
Quantitative ground glass			
mL			
Week 24	710.3 (298.61)	680.2 (245.57)	696.8 (274.50)
Change from baseline	-19.6 (112.24)	-47.2 (127.15)	-32.0 (119.07)
%			
Week 24	19.5 (7.04)	16.9 (6.66)	18.3 (6.94)
Change from baseline	0.2 (4.49)	-0.8 (4.14)	-0.2 (4.33)
Honeycomb			
mL			
Week 24	18.4 (24.10)	28.6 (52.06)	23.0 (39.21)
Change from baseline	-4.3 (21.94)	8.3 (41.67)	1.4 (32.68)
%			
Week 24	0.5 (0.68)	0.6 (0.96)	0.6 (0.81)
Change from baseline	-0.1 (0.59)	0.1 (0.90)	0.0 (0.75)
Total lung capacity			
Week 24 (L)	3.7 (0.85)	4.2 (0.98)	3.9 (0.93)
Change from baseline at week 24 (mL)	-114.2 (480.05)	-44.0 (326.51)	-82.7 (416.72)

bid Twice a day, *HRCT* High-resolution computed tomography, *qd* Once daily, *QLF* Quantitative lung fibrosis, *SD* Standard deviation

category, where fibrosis improvement is defined as QLF change from baseline < -2%. In the 100-mg bid treatment groups, the majority (80%-100%) of patients with improved QLF scores had improved KBILD scores at week 24. Furthermore, the majority (63%-67%) of patients who had stable/worse QLF scores did not show improvement in KBILD. The pattern was less pronounced in the 50-mg qd treatment group.

Mean changes over time in KBILD total and domain scores by QLF improvement for each dose group are shown in Fig. 4. Patients in the 100-mg bid group with improved QLF showed an increase in KBILD total scores over time. Both the breathlessness and activities domain and psychological domain contributed to this improvement. Differences are apparent as early as week 8 and maintained through week 48 in the 100-mg bid group. At week 48, the mean change from baseline for the patients in the 100-mg bid group with improved QLF was 22.0 (SD 18.6) for KBILD total score and 31.4 (SD 23.0) for breathlessness and activities, 9.2 (SD 16.7) for chest symptoms, and 25.2 (SD 21.6) for psychological factors, all of which were greater than the MCID of 5 for KBILD.

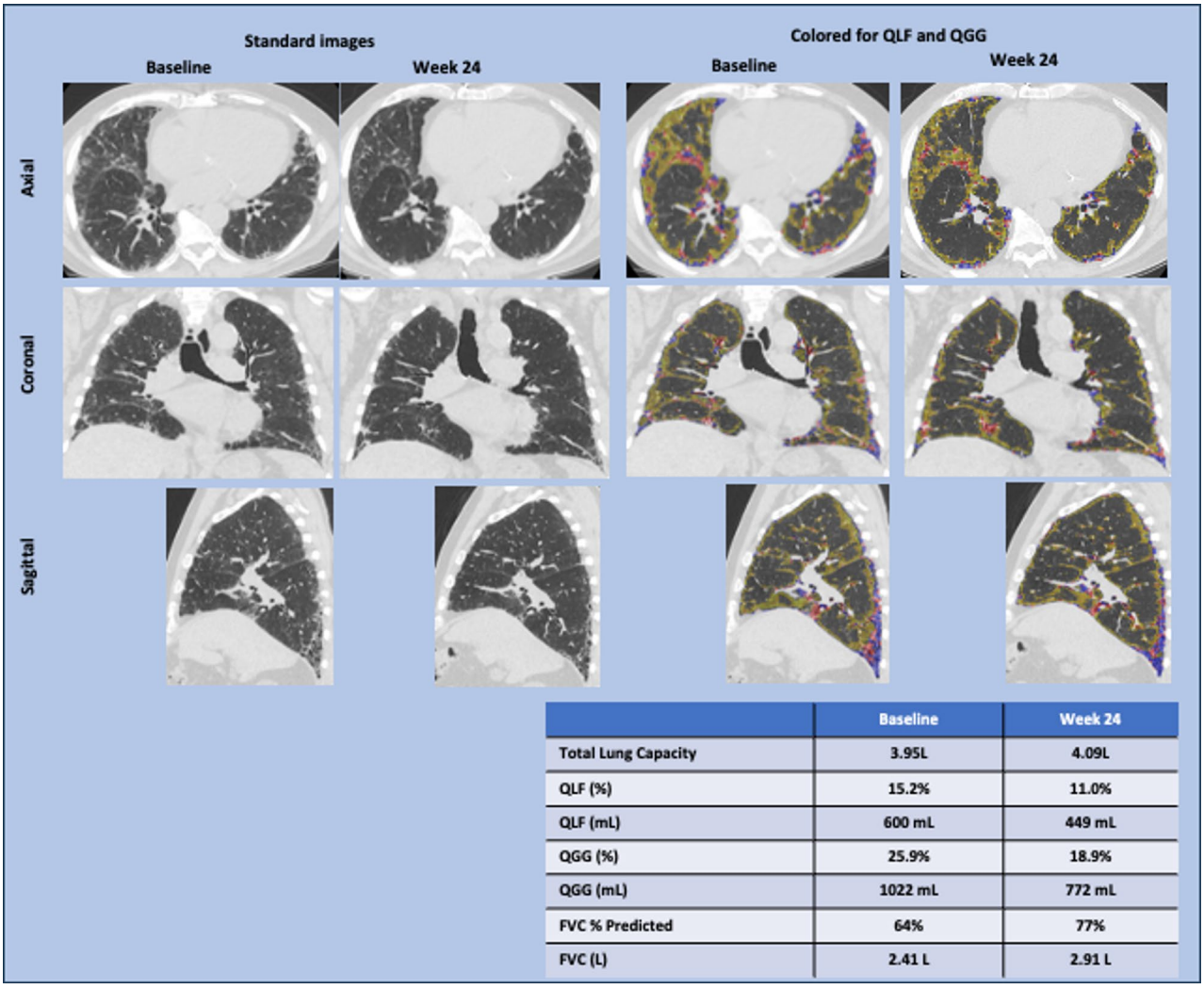
Discussion

We report the effect of the inhaled therapy AP01 in a phase 1b study of two dosing regimens on changes in the extent of fibrosis and lung volumes obtained from quantitative evaluation of HRCT and in QOL scores in patients with IPF. With the association of structural and functional changes having been previously reported [5], the post-hoc analyses presented here show correlation of the structural improvements quantified in the QLF scores with symptomatic improvements assessed by PRO measures. As measured by QLF score, the extent of fibrosis stabilised in some patients after treatment with AP01 and decreased in a few. Additional data supported the observed changes in fibrosis. Increases in fibrosis, as measured by HRCT, were smaller in the 100-mg bid group than in the 50-mg qd group.

Quantitative evaluation of HRCT has been incorporated as an outcome measure in several recent trials of antifibrotic agents in IPF. Patients treated with nintedanib or pamrevlumab, an investigational antifibrotic agent, demonstrated smaller increases in fibrosis as measured by HRCT than those treated with a placebo control. Lancaster et al. reported an increase from baseline in the adjusted mean QLF score of 21.7 mL for nintedanib, compared with 37.3 mL for the placebo group (Spearman correlation – 0.63) [11]. Richeldi et al. reported an increase of 24.5 mL for pamrevlumab, compared with 86.7 mL for the placebo group (Spearman correlation – 0.45) [10]. The increase of 25.8 mL in the AP01 50-mg qd group in this study is comparable to the active agents in Lancaster et al. and Richeldi et al. and smaller than their reported adjusted placebo means [10, 11]. Additionally, a decrease in mean QLF score of 29.5 mL in the 100-mg bid dose group was observed in this study, suggesting a reduction in fibrosis that was not reported for nintedanib or pamrevlumab [12].

Five patients (16%) on the higher 100-mg bid dose with an improvement in QLF scores at 24 weeks showed an early and sustained improvement in the validated KBILD score, which exceeded the MCID. To our knowledge, this is the first time an improvement in QLF scores has been significantly associated with an improvement in QOL.

In addition to the previously reported correlation between change in QLF score (mL) and change in FVC at 24 weeks in the 100-mg AP01 group [5], the analyses reported here show early structural changes at 24 weeks indicated by QLF score aligned with the symptomatic improvement reported at Week 48. Modest correlations were observed for the 50-mg qd group. The magnitude of improvement in QLF revealed by HRCT and in



	Baseline	Week 24
Total Lung Capacity	3.95L	4.09L
QLF (%)	15.2%	11.0%
QLF (mL)	600 mL	449 mL
QGG (%)	25.9%	18.9%
QGG (mL)	1022 mL	772 mL
FVC % Predicted	64%	77%
FVC (L)	2.41 L	2.91 L

Fig. 2 Baseline and week 24 images of a 100-mg bid patient showing improved QLF and FVC. bid = twice a day; FVC = forced vital capacity; HRCT = high-resonance computed tomography; QLF = quantitative lung fibrosis; QGG = quantitative ground glass. The images in the left two columns are the standard axial, coronal, and sagittal HRCT images for an individual patient treated with AP01 100 mg bid. The images in the right two columns are the overlaid qualitative results of the corresponding images. Blue dots indicate the results of QLF classification; yellow dots indicate results for QGG

symptomatic changes revealed by KBILD scores was pronounced in the 100-mg bid group.

Our study included several limitations, which may impact the interpretation of the results. These limitations include the relatively small sample size and the absence of a placebo control. In addition, some post-baseline HRCT scans were conducted earlier than scheduled because of early terminations or later than planned because of 2020–2021 COVID-19 pandemic restrictions. Some post-baseline studies were never completed. Finally, site-determined evidence for UIP may have been heterogeneous. Despite these limitations, the stabilization or even decrease in the extent of fibrosis in some patients was encouraging, as was the inverse correlation between QLF score and FVC, consistent with earlier studies. Together, these results indicate that further investigation of AP01 is merited and support the continued use of quantitative evaluation of HRCT in IPF clinical trials.

Conclusions

The quantitative scores from HRCT support selection of the 100-mg bid clinical dose for further study. After treatment with AP01 in this phase 1b study of patients with IPF, the extent of fibrosis as measured by HRCT stabilised in some patients and decreased in a few. The 100-mg bid group showed smaller increases in fibrosis on average than the 50-mg qd group. Composition data supported the observed changes in fibrotic progression. Patients in the 100-mg bid group with improved QLF scores showed improvement in KBILD scores, with the total scores improving more than 20 points from baseline by week 48. Associations between changes in FVC,

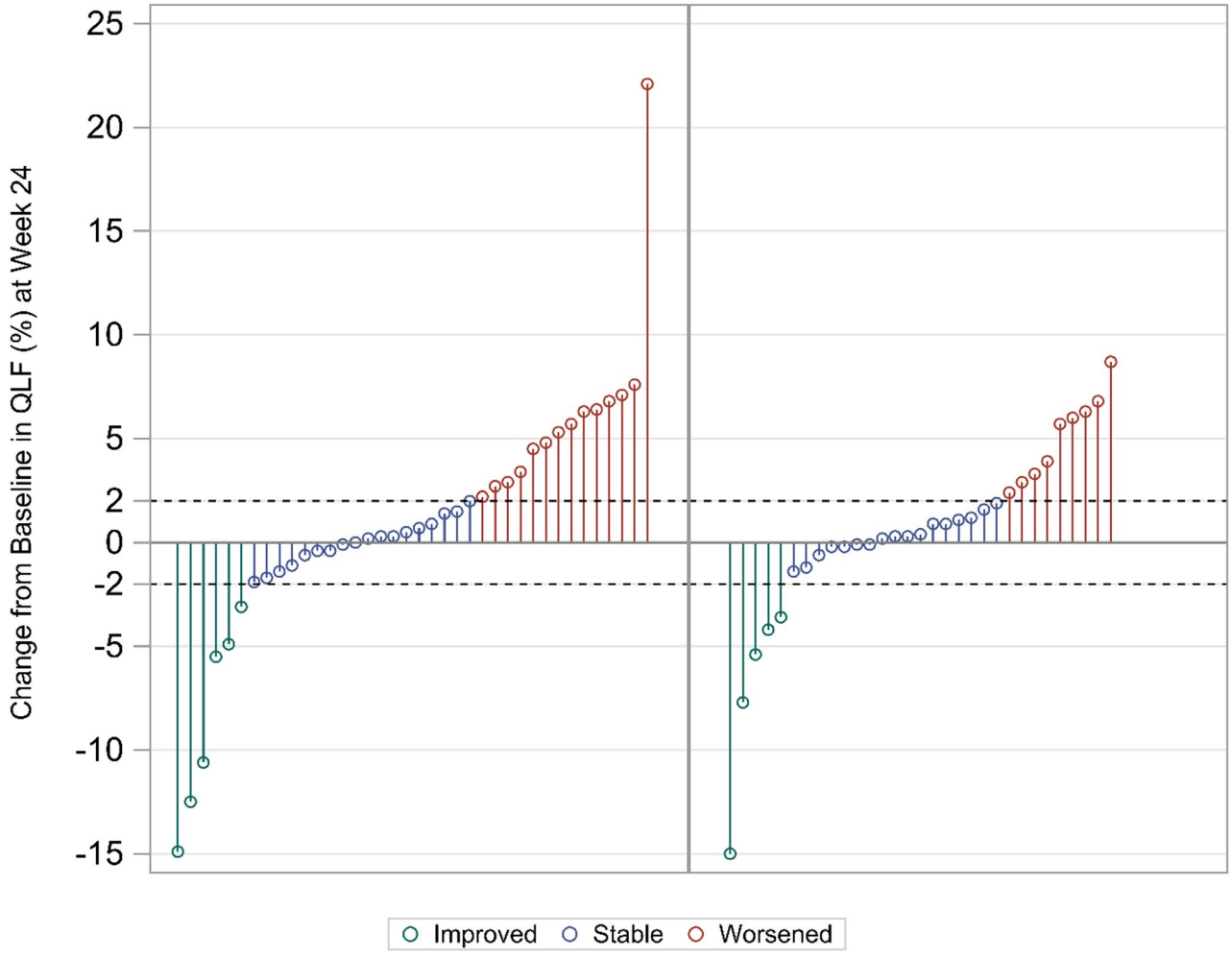


Fig. 3 Waterfall plot of change in QLF at week 24 as a percentage of whole lung by 50 mg qd (left) and 100 mg bid (right), bid = twice per day; qd = once per day; QLF = quantitative lung fibrosis

Table 3 KBILD improvement from baseline by HRCT improvement from baseline

	KBILD score change from baseline at week 24							
	Total score		**B & A score**		**Chest symptom score**		**Psychological score**	
	< 5	**≥ 5**	**< 5**	**≥ 5**	**< 5**	**≥ 5**	**< 5**	**≥ 5**
	50 mg qd (*N*=37[a])							
Improved[b] QLF at week 24 (n = 6)	3 (50%)	3 (50%)	5 (83.3%)	1 (16.7%)	2 (33.3%)	4 (66.7%)	2 (33.3%)	4 (66.7%)
Stable/worse[c] QLF at week 24 (*n* = 31)	27 (87.1%)	4 (12.9%)	26 (83.9%)	5 (16.1%)	20 (64.5%)	11 (35.5%)	22 (71.0%)	9 (29.0%)
	100 mg bid (*N* = 31)							
Improved[b] QLF at week 24 (*n* = 5)	1 (20%)	4 (80%)	0	5 (100%)	2 (40%)	3 (60%)	1 (20%)	4 (80%)
Stable/worse[c] QLF at week 24 (*n* = 24)	16 (66.7%)	8 (33.3%)	15 (62.5%)	9 (37.5%)	15 (62.5%)	9 (37.5%)	16 (66.7%)	8 (33.3%)

B & A Breathlessness and activities, *bid* Twice a day, *KBILD* King's Brief Interstitial Lung Disease questionnaire, *qd* Once daily, *QLF* Quantitative lung fibrosis

[a]Analysis includes patients with week 24 data

[b]QLF improvement defined as < -2.0% change from baseline

[c]QLF stable and worse defined as ≥ -2.0 to ≤ 2% and> 2%, respectively

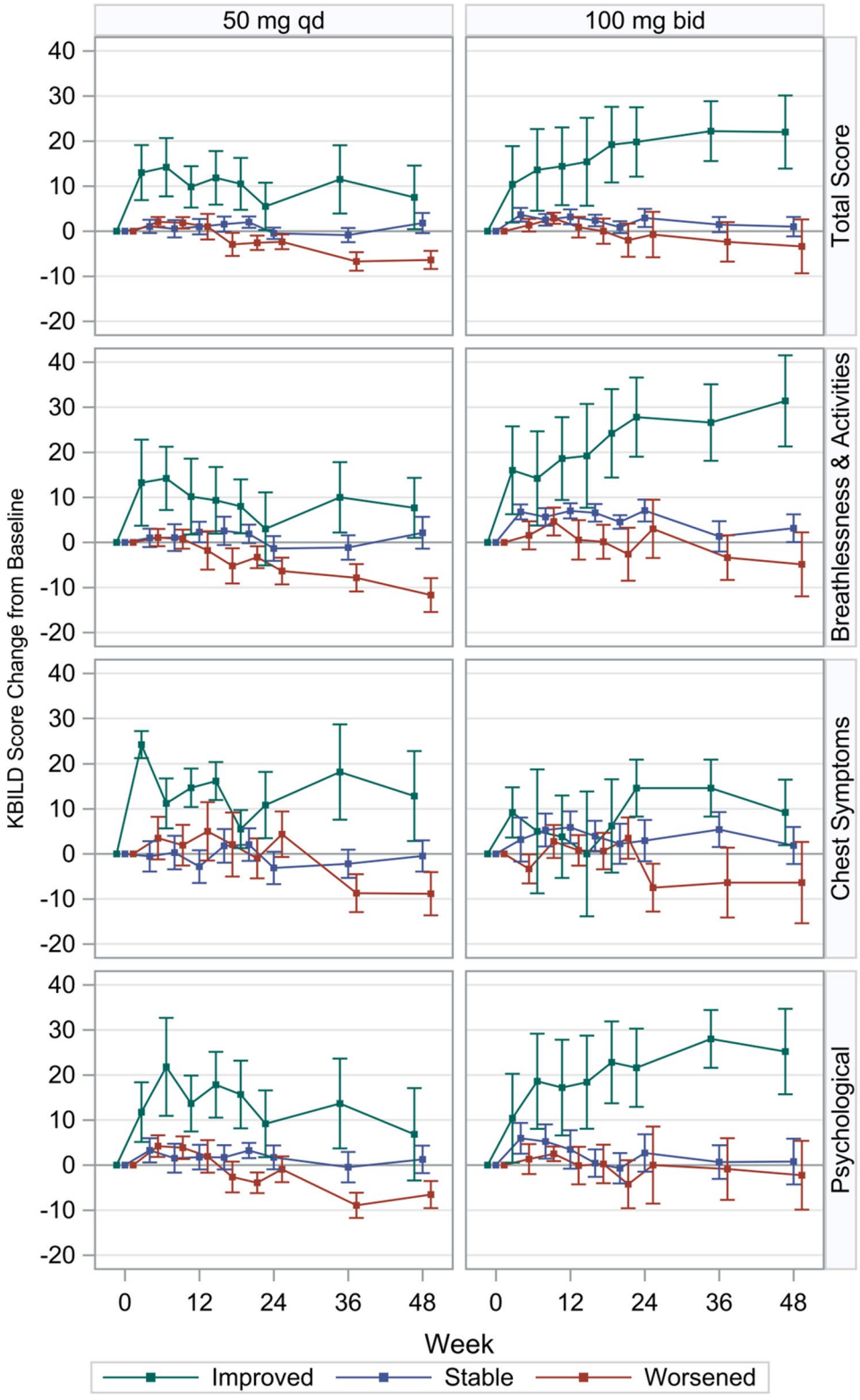


Fig. 4 KBILD change from baseline by category of change in QLF (% of whole lung). bid = two times per day; KBILD = King's Brief Interstitial Lung Disease questionnaire; qd = once per day; QLF = quantitative lung fibrosis

KBILD, and QLF confirm the functional, symptomatic, and structural changes in IPF patients. Furthermore, they support the 100-mg bid dose moving forward into the next AP01 study.

With continued follow-up of HRCT scans, our data suggest that the association between the QLF imaging biomarker and supportive physiological and QOL measures in the 100-mg bid dose may provide additional supportive data on dose-ranging for future studies. The results appear to be encouraging in the context of results from other recent trials of antifibrotic agents, such that further investigation of AP01 is merited.

Abbreviations

AP01	Inhaled pirfenidone
ATS	American Thoracic Society
bid	Twice a day
COVID-19	Coronavirus disease 2019
ERS	European Respiratory Society
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
IPF	Idiopathic pulmonary fibrosis
KBILD	The King's Brief Interstitial Lung Disease
LCQ	Leicester Cough Questionnaire
MCID	Minimally clinically important difference
PRO	Patient-reported outcome
QCT	Quantitative computed tomography
QGG	Quantitative ground glass
QHC	Quantitative honeycomb
QLF	Quantitative lung fibrosis
QOL	Quality of life
qd	Once daily
TLC	Total lung capacity
UIP	Usual interstitial pneumonia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-026-04234-x.

Supplementary Material 1.

Authors' contributions

Corresponding author JGG takes responsibility for the content of the manuscript, including the data and analysis. All authors have made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; drafted the work or reviewed it critically for important intellectual content; given final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GHJK and FAW were responsible for conception/design of the manuscript; DN and CSC were involved in data acquisition; FAW, DN, HB, HML, and CSC participated in data analysis; and GHJK, FAW, HML, and CSC contributed to data interpretation. JGG participated in conception/design of the manuscript as well as data acquisition, analysis, and interpretation.

Funding

Avalyn Pharma Inc. sponsored this study and participated in the study design, analysis, interpretation of data, writing and revision of this paper, and decision to submit it for publication. Editorial and writing support were provided by Acumen Medical Communications, LLC and funded by Avalyn Pharma Inc.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

GHJK holds Patent UC-2013-078-2-LA-EP and has received consulting fees from Voiant and a research grant fund from Boehringer Ingelheim. FAW and CSC are employees of Avalyn Pharma Inc. and hold stock options. DN, HB, and HML are employees of Avalyn Pharma Inc. JGG reports receiving support for his written contributions to the present manuscript from Avalyn Pharma Inc., consulting fees and support for travel to meetings from Boehringer Ingelheim (education advisory board), and consulting fees from Zura. He is also a named inventor on a UCLA-owned patent (UC Patent UC-20132-078-2-LA-US, 2015) and holds stock/stock options in MedQIA.

Ethics approval and consent to participate

Local Ethics Committees/Institutional Review Boards approved the protocol for each site, and all patients provided written informed consent before enrolment. A table presenting Ethics Committees/Institutional Review Boards and approval IDs/numbers is provided in Supplemental Table 1.

Consent for publication

Not applicable.

Competing interests

GHJK holds Patent UC-2013-078-2-LA-EP and has received consulting fees from Voiant and a research grant fund from Boehringer Ingelheim. FAW and CSC are employees of Avalyn Pharma Inc. and hold stock options. DN, HB, and HML are employees of Avalyn Pharma Inc. JGG reports receiving support for his written contributions to the present manuscript from Avalyn Pharma Inc., consulting fees and support for travel to meetings from Boehringer Ingelheim (education advisory board), and consulting fees from Zura. He is also a named inventor on a UCLA-owned patent (UC Patent UC-20132-078-2-LA-US, 2015) and holds stock/stock options in MedQIA.

Received: 27 November 2024 / Accepted: 6 March 2026
Published online: 23 March 2026

References

1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68.
2. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
3. Clarke SW, Newman SP. Therapeutic aerosols 2–Drugs available by the inhaled route. Thorax. 1984;39(1):1–7.
4. Khoo JK, Montgomery AB, Otto KL, Surber M, Faggian J, Lickliter JD, 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(1):15–20.
5. West A, Chaudhuri N, Barczyk A, Wilsher ML, Hopkins P, Glaspole I, et al. Inhaled pirfenidone solution (AP01) for IPF: a randomised, open-label, dose-response trial. Thorax. 2023;78(9):882–9.
6. U.S.Food and Drug Administration (FDA). Multiple Endpoints in Clinical Trials: Guidance for Industry. Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2022. https://www.fda.gov/media/162416/download.
7. Raghu G, Ghazipura M, Fleming TR, Aronson KI, Behr J, Brown KK et al. Meaningful Endpoints for Idiopathic Pulmonary Fibrosis (IPF) clinical trials: emphasis on 'feels, functions, survives'. report of a collaborative discussion in a symposium with direct engagement from representatives of patients, investigators, the national institutes of health, a patient advocacy organization, and a regulatory agency. Am J Respir Crit Care Med. 2024;209(6):647 – 69.
8. Lynch DA, Godwin JD, Safrin S, Starko KM, Hormel P, Brown KK, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005;172(4):488–93.
9. Wu X, Kim GH, Salisbury ML, Barber D, Bartholmai BJ, Brown KK, et al. Computed Tomographic Biomarkers in Idiopathic Pulmonary Fibrosis. The Future of Quantitative Analysis. Am J Respir Crit Care Med. 2019;199(1):12–21.

10. Richeldi L, Fernandez Perez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, et al. Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2020;8(1):25–33.
11. Lancaster L, Goldin J, Trampisch M, Kim GH, Ilowite J, Homik L, et al. Effects of Nintedanib on Quantitative Lung Fibrosis Score in Idiopathic Pulmonary Fibrosis. Open Respir Med J. 2020;14:22–31.
12. Kim GHJ, Goldin JG, Hayes W, Oh A, Soule B, Du S. The value of imaging and clinical outcomes in a phase II clinical trial of a lysophosphatidic acid receptor antagonist in idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2021;15:17534666211004238.
13. Kim HG, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol. 2010;28(5 Suppl 62):S26–35.
14. Wang XTP, Lo P, Banola A, Kim G, Abtin F, Goldin J, Brown M. High Throughput Lung and Lobar Segmentation by 2D and 3D CNN on Chest CT with Diffuse Lung Disease. In: Stoyanov D, et al. editors. Image Analysis for Moving Organ, Breast, and Thoracic Images. RAMBO BIA TIA 2018. Lecture Notes in Computer Science. Cham: Springer; 2018. p. 202–214.
15. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339–43.
16. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012;67(9):804–10.
17. Sinha A, Patel AS, Siegert RJ, Bajwah S, Maher TM, Renzoni EA, et al. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. BMJ Open Respir Res. 2019;6(1):e000363.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.