Nebulized Pirfenidone (APO1) for Progressive Pulmonary Fibrosis in Connective Tissue Disease-associated and Other Interstitial Lung Diseases: 4-year Data from the ATLAS Open Label Extension Trial

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BACKGROUND

- Oral pirfenidone, approved for use in idiopathic pulmonary fibrosis (IPF), is associated with gastrointestinal, dermatologic, and systemic side effects, which can lead to dose modifications, interruptions, and/or discontinuations, thus impacting potential efficacy.[1-4]
- While pirfenidone is not currently approved for use in progressive pulmonary fibrosis (PPF), the 2025 ERS/EULAR guidelines for connective tissue disease related interstitial lung diseases (CTD-ILDs) conditionally recommend pirfenidone in rheumatoid arthritis-associated ILD (RA-ILD) with a usual interstitial pneumonia (UIP) pattern. The guidelines provide no recommendation for its off-label use in other CTD-ILDs or PPF due to limited evidence, though three academic studies evaluating oral pirfenidone in PPF populations suggest potential activity.[5-8]
- APO1, an optimized nebulized formulation of pirfenidone delivered via the eFlow® Nebulizer System (**Figure 1**), was designed to enable targeted delivery to affected lung tissue. This approach aims to achieve higher lung exposure and lower systemic exposure, thereby potentially improving both activity and tolerability.
- APO1 has been studied in the IPF population in the ATLAS Phase 1b trial (ACTRN12618001838202) and in both the IPF and PPF populations in the ATLAS open-label extension trial (OLE; EudraCT 2020-005103-39).[9,10]

Figure 1: Depiction of eFlow nebulizer use

OBJECTIVE

- To report data on the PPF cohort treated with nebulized pirfenidone (APO1) from the ATLAS OLE study.

METHODS

- The ATLAS OLE study was conducted from 2021-2025. It enrolled patients with IPF from the ATLAS trial who continued APO1, while also allowing for the inclusion of two new cohorts of patients with compassionate use in mind: a second group with IPF, and a group with PPF meeting defined progression criteria. We present data herein for the PPF cohort.
- All patients received APO1 100mg twice daily (BID).
- Safety outcomes were evaluated. While efficacy outcome measures were not study endpoints per protocol, forced vital capacity (FVC) data were captured and compared to baseline measurements and placebo-group trajectories from other trials in PPF.[11,12]
- Safety and lung function data were collected at clinic visits every 12 weeks.

RESULTS

BASELINE CHARACTERISTICS

- Twenty-eight participants (n=28) in the ATLAS OLE study had PPF (**Table 1**).

Table 1: Demographics and baseline characteristics of the PPF cohort in the ATLAS OLE study

Demographic/Baseline Characteristic	(N=28)
Age (years), median (range)	65 (31-81)
Female, n (%)	16 (57.1)
White, n (%)	28 (100)
Former smoker, n (%)	11 (39.3)
Current smoker, n (%)	1 (3.6)
Time from PPF diagnosis to baseline (years), median (IQR)	2.5 (1-4.7)
FVC (L), median (IQR)	2.5 (1.9-3)
FVC % predicted, median (IQR)	73 (62.5-88)
Severe respiratory impairment †, n (%)	11 (39.3)
Moderate respiratory impairment †, n (%)	8 (28.6)
Mild respiratory impairment †, n (%)	9 (32.1)

IQR: Interquartile Range. † Severe respiratory impairment defined by FVC ≤ 65% predicted; moderate respiratory impairment defined by FVC >65% and <80% predicted; and mild respiratory impairment defined by FVC ≥80% predicted.

BASELINE CHARACTERISTICS (Continued)

- Underlying diagnoses of all 28 participants with PPF are outlined in **Table 2**. Ten participants (35.7%) with PPF had a CTD diagnosis.
- The majority of participants with PPF (n=18, 64.3%) were receiving concomitant corticosteroids and 3 (10.7%) were on background nintedanib (**Table 3**).

Table 2: Underlying diagnoses of participants with PPF in the ATLAS OLE study

Underlying Diagnosis *	Participants (N=28), n (%)
Connective Tissue Diseases	10 (35.7)
Rheumatoid arthritis	3 (10.7)
Antisynthetase syndrome	2 (7.1)
Systemic sclerosis	2 (7.1)
Sjögren's syndrome	2 (7.1)
Undifferentiated connective tissue disease	1 (3.6)
Non-Connective Tissue Diseases	18 (64.3)
Non-hypersensitivity pneumonitis pattern	8 (28.6)
Hypersensitivity pneumonitis	6 (21.4)
Interstitial pneumonia with autoimmune features	3 (10.7)
Asbestosis	1 (3.6)

Table 3: Prescribed concomitant corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and antifibrotics among participants with PPF in the ATLAS OLE study

Concomitant Corticosteroids, DMARDs & Antifibrotics	Participants (N=28), n (%)
Corticosteroids	18 (64.3)
Mycophenolate mofetil	8 (28.6)
Hydroxychloroquine	4 (14.3)
Nintedanib	3 (10.7)
Tocilizumab	3 (10.7)
Methotrexate	2 (7.1)
Leflunomide	2 (7.1)
Sulfasalazine	1 (3.6)
Rituximab	1 (3.6)
Pirfenidone **	1 (3.6)

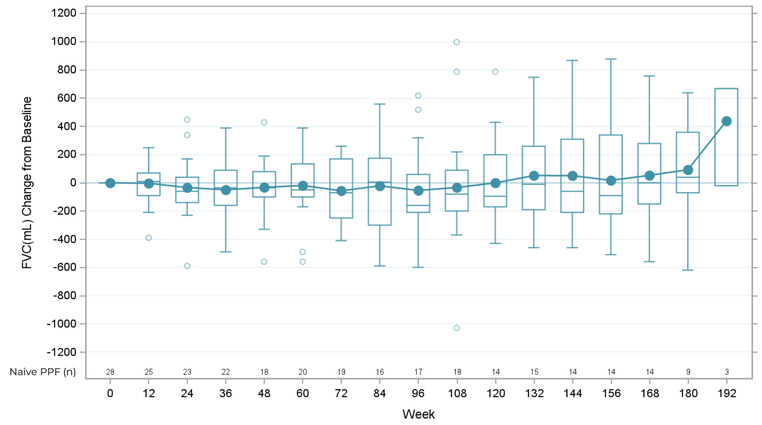
OUTCOMES

- Median duration of therapy was 39 months. Fourteen patients received therapy for ≥42 months, with 3 patients receiving therapy for the maximum duration of 48 months.
- APO1 was well tolerated in the PPF cohort, with no notable differences in the safety profile from the IPF cohort.[13] Treatment-related adverse events of cough and decreased appetite were reported in >1 participant (**Table 4**). No other TEAEs were reported by more than 1 participant. Of note, only one (3.6%) participant reported treatment-related diarrhea and one (3.6%) reported treatment-related rash.
- At Week 48, the mean change from baseline FVC was -31.7 mL, compared to -165 mL in the FIBRONEER-ILD at Week 52, and -187.8 mL/year mean rate of decline at Week 52 in the INBUILD study placebo groups, respectively.***[11,12] **Figure 2** displays box plots of FVC (mL) change from baseline of the PPF cohort over 192 weeks.

Table 4: Summary of Treatment-Related Treatment-Emergent Adverse Events (TEAEs) in >1 participants with PPF in the ATLAS OLE study

Treatment-Related TEAEs Reported in >1 Participants with PPF	Participants (N=28), n (%)
Cough	3 (10.7)
Decreased appetite	2 (7.1)

Figure 2: Mean, median, and quartiles of FVC(mL) change from baseline of the PPF cohort in the ATLAS OLE study



CONCLUSIONS

- In the 4-year ATLAS OLE study, nebulized pirfenidone (APO1) was well tolerated in patients with PPF, including those with CTD-ILDs on a variety of concomitant medications, including DMARDs.
- Though this study was not designed to evaluate efficacy outcomes, APO1 showed a favorable FVC trajectory among patients with PPF relative to placebo groups from other completed year-long studies in PPF populations.
- APO1 is now being studied in the MIST study (NCT06329401), a Phase 2b, randomized, placebo-controlled trial for patients with PPF, with study completion expected in 2027.

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* For improved clinical interpretation, verbatim diagnosis text written by the investigators has been categorized as follows: rheumatoid arthritis includes fibrosing phenotype ILD (n=2) and rheumatoid lung (n=1); antisynthetase syndrome includes fibrosing phenotype ILD (n=1) and PL-7 positive antisynthetase syndrome (n=1); systemic sclerosis includes connective tissue disease related interstitial lung disease (n=1) and pulmonary involvement of scleroderma (n=1); Sjögren's syndrome includes fibrosing phenotype ILD (n=1) and Sjögren syndrome with progressive pulmonary fibrosis (n=1); undifferentiated connective tissue disease includes connective tissue disease interstitial lung disease (n=1); non-hypersensitivity pneumonitis pattern includes fibrosing phenotype ILD (n=6), non-specific interstitial pneumonia (n=1), and unclassifiable (n=1); hypersensitivity pneumonitis includes chronic hypersensitivity pneumonitis (n=2) and fibrosing phenotype ILD (n=4); interstitial pneumonia with autoimmune features includes autoimmune lung fibrosis (n=1), fibrosing phenotype ILD (n=1), and interstitial pneumonia with autoimmune features (n=1); and asbestosis includes asbestosis (n=1).

** One subject took oral pirfenidone for a total of 5 days from Study Day 499 to Study Day 504.

*** The Week 48 change from baseline in PPF subjects of -31.7 mL for the ATLAS OLE study is the observed mean change from baseline at Week 48. We compare this change from baseline to the -187.8 mL/year slope result for the PPF placebo subjects in INBUILD, based on a random intercept and slope model, and to the -165.8 mL Mixed-Effects for Repeated Measures model-adjusted mean change from baseline at 1 year for the PPF placebo subjects in the FIBRONEER-ILD study. Both INBUILD and FIBRONEER-ILD were one-year studies.

DISCLOSURES:

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