Cough adverse events and FVC decline in the ATLAS study of inhaled pirfenidone (AP01) in idiopathic pulmonary fibrosis

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ILD/DPLD of known origin
Idiopathic pulmonary treatments
Diagnosis

INTRODUCTION

- Cough is a common Adverse Event (AE) in Idiopathic Pulmonary Fibrosis (IPF) trials.
- Pooled trials showed rates of 23.1% on oral pirfenidone and 24% on placebo[1].
- Cough has been found to be independently-associated with progression of IPF[2].

AIMS

- To examine the relationship between cough AE and disease progression in the open-label ATLAS study[3] of inhaled pirfenidone–AP01 50mg once (qd) or 100mg twice daily (bid) in IPF.

METHODS

- This phase 1b, randomized, open-label, dose-response trial assessed the safety, tolerability, and efficacy of inhaled pirfenidone (AP01) in IPF.
- Patients with forced vital capacity (FVC) 40%–90% predicted, and intolerant, unwilling, or ineligible for oral pirfenidone or nintedanib were randomized to nebulized AP01 50 mg once per day or 100 mg two times per day for 24 weeks.
- Leicester Cough Monitor (LCM) counts over 24 hours were assessed at baseline, week 12, and week 24.
- Cough Visual Analogue Score (VAS) and Leicester Cough Questionnaire (LCQ) were recorded every 4 weeks.
- FVC change from baseline was modeled by linear slopes.

RESULTS

	50 mg qd		100 mg bid	
	Overall (n=46)	**Cough AE (n=11) No Cough AE (n=35)**	**Overall (n=42)**	**Cough AE (n=13) No Cough AE (n=29)**
Baseline LCM Median (Q1-Q3)	8.25 (3.80-18.20)	13.55 (5.00-17.40) 7.75 (3.50-19.00)	7.80 (3.90-17.50)	7.50 (4.80-13.70) 10.10 (3.90-17.50)
12 Week LCM Median (Q1-Q3)	7.70 (4.00-13.60)	7.90 (4.80-13.60) 7.50 (3.00-15.40)	7.40 (4.10-23.50)	5.20 (1.65-25.50) 7.85 (4.80-15.50)
24 Week LCM Median (Q1-Q3)	8.35 (2.85-12.05)	9.00 (6.45-11.90) 7.75 (2.70-13.20)	8.40 (2.85-20.75)	7.50 (5.10-17.70) 8.50 (2.50-23.50)
Estimated Slope mL/year (95% CI)	-188 (-277, -99)	-206 (-355, -58) -182 (-293, -71)	-34 (-127, 60)	-129 (-272, 14) 1 (-120, 122)
Difference (AP01 100 mg bid – AP01 50 mg qd) mL/year (95% CI)	Cough No Cough Overall	77 (-129, 283), p=0.4357 183 (19, 347), p=0.0301 154 (25, 284), p=0.0203		

Table 1. Leicester Cough Monitor Counts and Forced Vital Capacity Decline.
Abbreviations: AE=adverse event; bid=twice daily; CI=confidence interval; LCM=Leicester Cough Monitor 24-hour Hourly Count; qd=once daily.

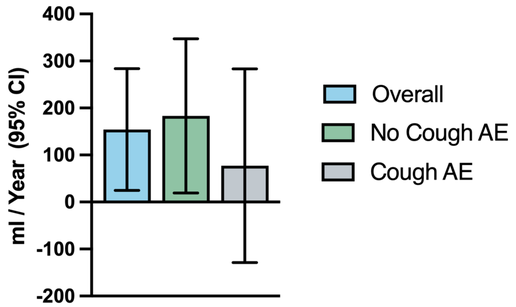

Figure 1. Forced Vital Capacity Estimated Slope Difference calculated from AP01 100 mg bid – AP01 50 mg qd.
Abbreviations: AE=adverse event; bid=twice daily; CI=confidence interval; FVC=forced vital capacity; qd=once daily.

SUMMARY

- Cough AEs occurred in 11/46 (24%) on 50mg qd & 13/42 (31%) on 100mg bid.
- LCM counts were similar for both doses, with or without a cough AE, and remained stable over time (**Table 1**). The same was true for VAS and LCQ (not shown).
- Estimated slope FVC mL/year overall was -188 for 50mg qd and -34 for 100mg bid with a difference of 154 mL, p = 0.0203.
- FVC decline was more pronounced in those with an AE of cough (-206, 50mg qd, & -129 mL, 100 mg bid).

CONCLUSIONS

- There was no objective difference in cough counts between the two dose regimes and no significant change over time.
- Amongst subjects on 100mg bid, progression was worse in those with a cough AE than those without.
- Whilst there was a significant difference in annual FVC decline between doses and in those without a cough AE, this was not the case in those with a cough AE.
- It is unclear if this is a general feature of IPF and would bear examination in other cohorts, including patients with progressive pulmonary fibrosis (PPF).

1. Noble, P. W. et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. European Respiratory Journal ERJ-00026 (2015).
2. Ryerson, C. J. et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology 16, 969–975 (2011).
3. West, A. et al. Inhaled pirfenidone solution (AP01) for IPF: a randomised, open-label, dose–response trial. Thorax (2023) doi:10.1136/thorax-2022-219391.

PRESENTING AUTHOR DISCLOSURE
The presenting author has no, real or perceived, conflict(s) of interest that relate to this abstract