Inhaled pirfenidone reduces the risk of disease progression: a post-hoc analysis of the ATLAS study

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BACKGROUND

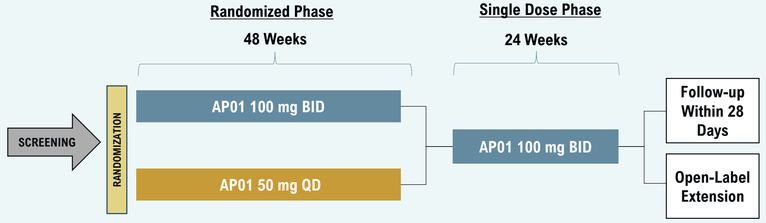
Oral pirfenidone reduces FVC decline compared to placebo in Idiopathic Pulmonary Fibrosis (IPF), albeit with side effects[1]. AP01 is an aqueous pirfenidone formulation optimized for nebulization and inhaled administration. A 100 mg of AP01 delivers pulmonary pirfenidone concentrations 35 times higher than that following an 801 mg oral dose with 1/15 the systemic exposure[2].

AP01-002 (ATLAS) was a two-part, 72 week open-label, Phase 1b study in IPF patients comparing 50 mg once daily with 100 mg twice daily[3]. There was no placebo arm. The study was conducted at 25 sites across 6 countries in 91 patients. An analysis of mortality amongst placebo subjects from the pivotal nintedanib and pirfenidone IPF trials was carried out by members of the FDA in 2017[4]. This showed that an FVC decline of >10% (but not 5-10%) was associated with a significantly-increased risk of mortality. Here we report findings from the ATLAS study using a 10% threshold of FVC decline.

METHODS

Study subjects were at least age 40 and possessed a confident diagnosis of IPF. Main inclusion criteria included FVC % predicted 40-90%; FEV_1/FVC ratio ≥70%; and DLco 30-90%. Eligible IPF patients were either unable to qualify for or tolerate oral pirfenidone and nintedanib. Patients were enrolled July 2019-April 2020, randomized 1:1 to either 50mg QD or 100mg BID. Observed proportions of subjects with a decline were compared between AP01 100 mg BID and AP01 50 mg QD arms using Fisher's exact test. Placebo results from Paterniti et al were referenced[4].

ATLAS STUDY DESIGN



RESULTS

ATLAS enrolled 91 patients (46 at 50 mg QD, 45 at 100 mg BID). Participants had baseline characteristics similar to oral pirfenidone Phase 3 studies, although ATLAS patients were older and had a longer duration of disease. By Week 48, 6 of 29 subjects (20.7%) receiving AP01 100 mg BID and 10 of 29 subjects (34.5%) receiving AP01 50 mg QD experienced a decline of >10% (p=0.3786) (Figure 1). While statistical significance was not noted, a demonstrable trend in reduction in the AP01 100 mg BID group vs the AP01 50 mg BID group was seen at each time point. In the placebo cohort, 34.0% declined by 10%. Adverse Events (AEs) reported for ≥ 10% of patients included nausea, rash, cough, fatigue, and upper respiratory tract infection (Figure 2).

BASELINE CHARACTERISTCS

Characteristic	50 mg QD (N=46)	100 mg BID (N=45)	Total (N=91)
Asia-Pacific Region, n (%)	21 (45.7)	21 (46.7)	42 (46.2)
Age (years), Mean (SD)	73.4 (7.03)	71.3 (8.08)	72.4 (7.60)
Female, n (%)	14 (30.4)	13 (28.9)	27 (29.7)
Former Smoker, n (%)	33 (71.7)	32 (71.1)	65 (71.4)
FVC % Predicted at Screening, Mean (SD)	71.4 (11.81)	72.1 (9.81)	71.7 (10.81)
FVC 40 to < 50% Predicted at Screening, n (%)	3 (6.5)	0	3 (3.3)
FVC ≥ 80% at Baseline, n (%)	15 (32.6)	14 (31.1)	29 (31.9)
DLCO % Predicted at Screening, Mean (SD)	48.6 (13.98)	49.1 (10.72)	48.8 (12.41)
Duration of Diagnosis (years), Mean (SD)	1.9 (1.29)	2.1 (1.44)	2.0 (1.36)
CT Pattern from Scan, n (%) Typical UIP Pattern Probable UIP Pattern Indeterminate Pattern	 14 (30.4) 31 (67.4) 1 (2.2)	 24 (53.3) 19 (42.2) 2 (4.4)	 38 (41.8) 50 (54.9) 3 (3.3)

FIGURE 1

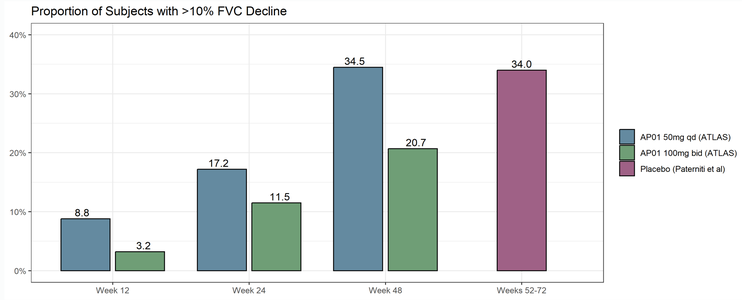
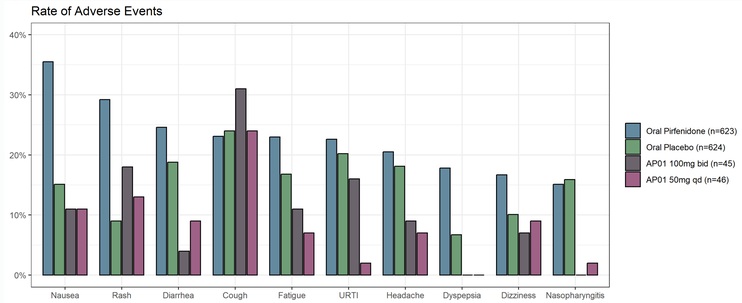


FIGURE 2



CONCLUSIONS

In the ATLAS study, there were fewer IPF patients in the AP01 100 mg BID arm compared to the 50 mg QD arm that experienced a greater than 10% FVC decline by 48 weeks. This is a threshold previously shown to predict increased mortality in patients with IPF. Similar numerical advantages were observed when comparing AP01 100 mg BID to published results for placebo from pivotal studies. These data support further evaluation of AP01 100 mg BID in studies of interstitial lung diseases.

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