AIR – an open-label, 36-week, clinical trial of buloxibutid – investigating the disease modifying potential of a novel angiotensin II type 2 receptor agonist in IPF

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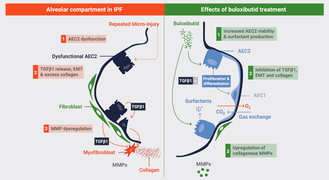
Background and rationale

Idiopathic pulmonary fibrosis (IPF) is a fatal disease with a huge unmet medical need. In addition to the progressive fibrosis formation, alveolar collapse is proposed to contribute to the loss of lung function.

Buloxibutid (C21) is an oral, selective angiotensin II type 2 receptor agonist, which drives an upstream repair pathway that improves alveolar epithelial type 2 cell (AEC2) survival and surfactant production, reduces fibrosis, and resolves vascular remodeling.

High-resolution CT (HRCT) scan patterns - Usual Interstitial Pneumonia (UIP) or probable UIP – have not been shown to affect the response to anti-fibrotics[1]. However, buloxibutid's novel mechanism of action improving AEC2 survival might be more powerful in probable UIP, where less alveoli are affected by severe fibrosis (honeycombing).

Buloxibutid is an oral, selective angiotensin II type 2 receptor (AT2R) agonist which drives an upstream repair pathway



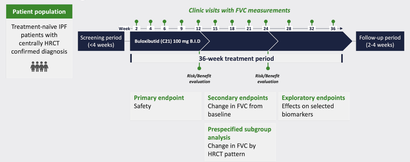
EMT = Epithelial–mesenchymal transition; MMPs = Matrix metalloproteinases

Methods

AIR was an open-label, single-arm, 36-week, phase 2a trial of buloxibutid 100 mg BID in treatment-naïve participants with IPF. The diagnosis was centrally confirmed through expert review of HRCT scans.

The primary outcome measure was safety. Efficacy was evaluated as change in forced vital capacity (FVC) from baseline, overall and in subgroups based on HRCT pattern. Plasma levels of TGF-β1 (Transforming Growth Factor beta 1) and the collagenase MMP-13 (Matrix Metalloproteinase-13) were measured as markers of mechanism.

Trial design



Results

52 participants with IPF (UIP 20, probable UIP 32) were enrolled and treated, and 28 participants completed the 36-week main trial period. Demographic and baseline characteristics were typical for an IPF population and similar between participants with UIP and typical UIP.

Baseline characteristics

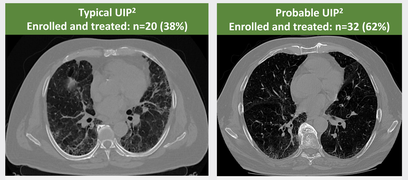
Baseline demographics

Characteristic		Typical UIP N=20	Probable UIP N=32
Age (years); mean (SD)		68.0 (8.1)	66.8 (10.2)
Gender	Male; n (%)	16 (80%)	24 (75%)
	Female; n (%)	4 (20%)	8 (25%)
Race	Asian; n (%)	15 (75%)	23 (72%)
	White; n (%)	5 (25%)	9 (28%)
Weight (kg); mean (SD)		61.2 (11.8)	66.8 (15.3)
Body mass index (kg/m²); mean (SD)		23.5 (3.70)	25.3 (4.28)

Baseline disease characteristics

Characteristic		Typical UIP N=20	Probable UIP N=32
Time since IPF diagnosis (years); mean (SD)		0.9 (1.09)	1.1 (1.27)
FVC	Mean - mL (SD)	2140 (295)	2541 (784)
	Median - mL	2210	2330
	% predicted; mean (SD)	69.3 (8.11)	79.3 (15.07)
FEV1/FVC ratio; mean (SD)		0.81 (0.069)	0.80 (0.067)
Oxygen saturation (%); mean (SD)		95.0 (2.4)	95.4 (2.4)
Previous use of anti-fibrotics		0 (0%)	0 (0%)

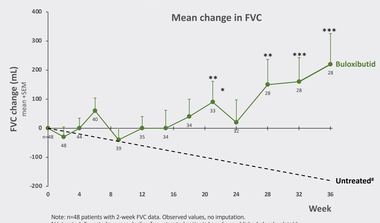
Central overread of HRCT scans



Male, Age 64, Baseline FVCpp: 61%

Male, Age 67, Baseline FVCpp: 87%

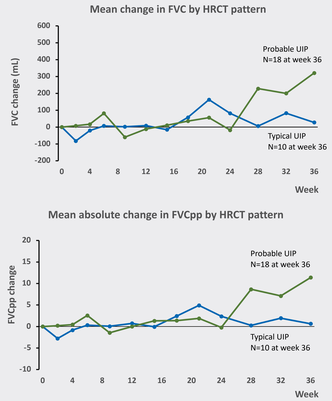
Stabilisation and improvement of FVC over 36 weeks



Note: n=48 patients with 2-week FVC data. Observed values, no imputation.
[4] Untreated: Expected average decline for untreated patients based on published placebo data[1,2].
*p<0.05, **p<0.01, ***p<0.001; t-test versus expected untreated decline corresponding to -120 mL/24 weeks

Mean FVC increased from baseline by 216 mL (90% CI +37, +395) at 36 weeks (n=28).

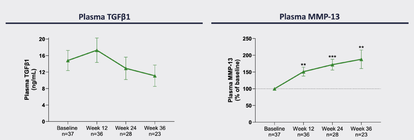
Stabilisation and improvement of FVC and FVCpp observed in both probable and typical UIP



Note: n=48 patients with 2-week FVC data. Observed values, no imputation.

At week 36, FVC increased from baseline by 27 mL (90% CI -216, +270) in patients with typical UIP (n=10), and by 321 mL (90% CI +73, +569) in patients with probable UIP (n=18). 72% of participants with probable UIP and 50% of participants with typical UIP had a positive change in FVCpp (FVC percent predicted) at week 36.

Effects on TGF-β1 and MMP-13 support FVC results



Note: data shown as mean ±SEM
** p<0.01, ***p<0.001 paired t-test vs baseline

There was a trend of reduction in TGF-β1. MMP-13 levels increased by >50% at weeks 24 and 36 (p<0.001 and 0.007, respectively).

Safety and tolerability summary

Treatment emergent adverse event (TEAE)	Buloxibutid 100 mg BID N=52 n (%)
Any TEAE	**37 (71.2)**
Related to trial drug	10 (19.2)
Serious TEAEs	**5 (9.6)**
Related to trial drug	0
Severe TEAEs	**3 (5.8)**
Related to trial drug	0
TEAEs leading to withdrawal of trial drug	**12 (23.1)**
Related to trial drug	3 (5.8)
TEAEs leading to discontinuation from trial	**6 (11.5)**
Related to trial drug	1 (1.9)
TEAEs leading to death	**2 (3.8)**
Related to trial drug	0

Most common TEAEs - any causality	Buloxibutid 100 mg BID N=52 n (%)
Hair loss	**10 (19.2)**
Rash	**4 (7.7)**
Cough	**4 (7.7)**
Gastro-esophageal reflux disease	**4 (7.7)**
Blood creatinine increased	**4 (7.7)**
Pyrexia	**4 (7.7)**

- No serious, fatal or severe adverse events related to buloxibutid
- Buloxibutid showed good gastrointestinal tolerability
- Hair loss was mild to moderate and reversible, one patient discontinued treatment due to hair loss

Conclusions

- Buloxibutid is an upstream intervention with a novel mechanism of action expected to drive tissue repair in IPF
- The safety profile shows excellent gastrointestinal tolerability and no treatment related serious adverse events.
- FVC stabilization and improvement, across IPF HRCT patterns, combined with reduction of plasma TGF-β1and increase of MMP-13, are consistent with the proposed mechanism of action of buloxibutid
- The pronounced FVC response across HRCT patterns, especially in probable UIP, may indicate a potential for IPF disease modification, explained by restoration of partially collapsed alveoli together with resolution of fibrosis.

[1] Raghu G., et al. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. Am J Respir Crit Care Med 2017;195:78–85.

[2] Raghu G., 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–e68

[3] Noble P.W., et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J. 2016;47:243–253

[4] Richeldi L., et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. New Engl J Med 2014;370:2071-2082

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