The novel angiotensin II type 2 receptor agonist buloxibutid improves lung function in IPF compared to real-world external IPF control arms

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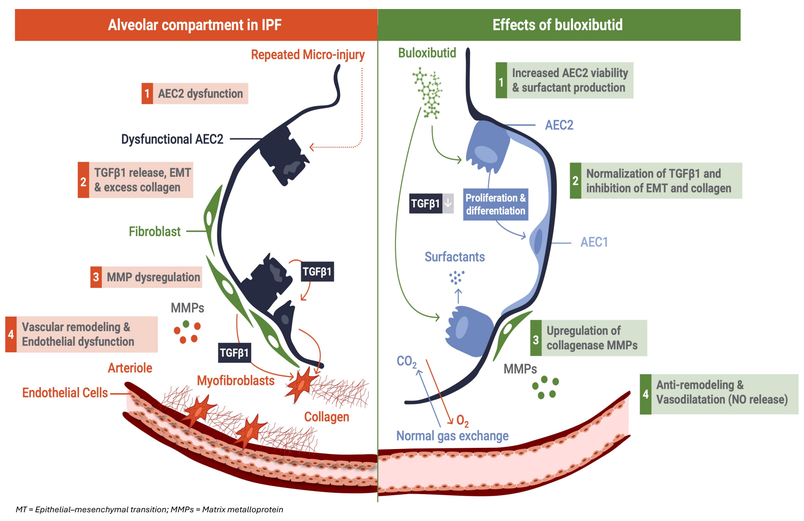
Background

Idiopathic pulmonary fibrosis (IPF) is a relentless, progressive and ultimately fatal interstitial lung disease, with an estimated prevalence of 8,500 to 9,300 people in Australia.

Buloxibutid (C21) is an oral, selective angiotensin II type 2 receptor (AT2R) agonist, which drives upstream repair pathways in idiopathic pulmonary fibrosis (IPF) that improve alveolar epithelial type 2 cell (AEC2) survival and surfactant production, reduces fibrosis, and resolves vascular remodeling.

Figure 1 – Buloxibutid Mechanism of Action



AIR was an open-label phase 2a trial of buloxibutid 100 mg BID in 52 treatment-naïve participants with IPF.

Figure 2 – Design of the AIR trial: An Open-Label, International, Phase 2a Trial of Oral Buloxibutid 100mg BID for Up to 36 Weeks in Naive IPF Patients

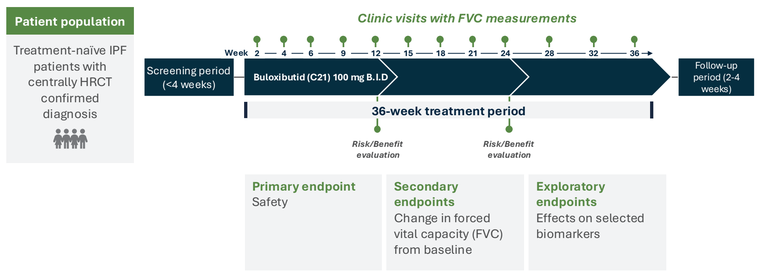
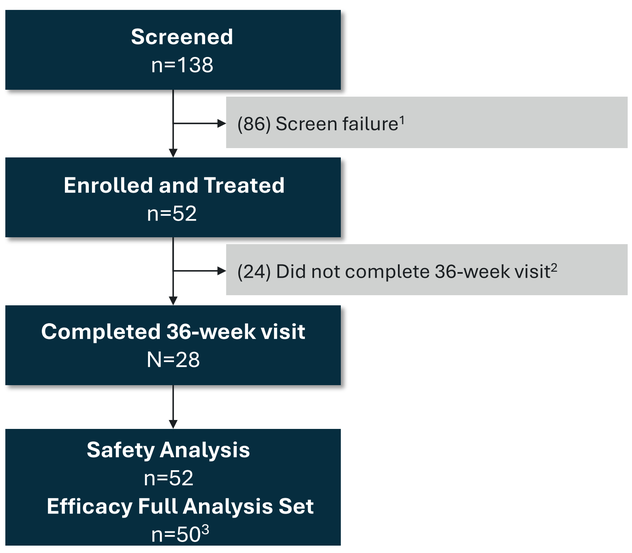


Figure 3 – Participant Flow in AIR



- Majority of discontinuations occurred before treatment week 12 and during COVID-19 pandemic
- Post week-12 discontinuation rate was 17%

[1]Did not meet inclusion criteria (73), met exclusion criteria (13)
[2]Death (2), other adverse event (5), FVC decline (3), patient decision (14)
[3]Excluding 2 patients with no post-baseline FVC data

Aims and Objectives

To explore the robustness of the findings in AIR, external synthetic control arms (SCAs) were generated using real-world IPF data from the Qureight platform.

Methods

Evaluable trial participants (n=48) were matched 1:1 with external controls based on 8 clinical variabes. Using Monte Carlo simulation, 408 individually matched SCAs were generated. Analyses were conducted using conservative imputation for missing data in the AIR cohort.

Figure 4 – Synthetic Control Arm (SCA) Generation

IPF Patient External Control Data
- Over 10,000 patients Mean 12-month FVC change -170.3 ml

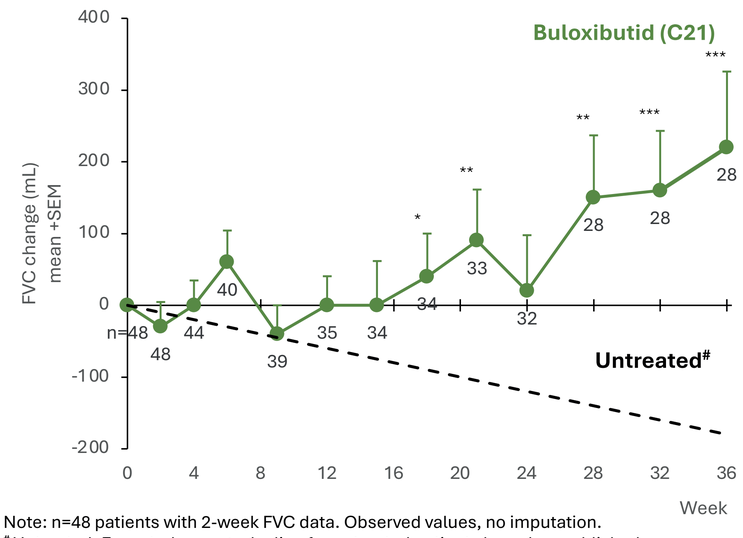
Filter IPF Patient Data using Air Trial Inclusion Criteria
- Age >= 40 years
- FVC % predicted >= 60%
- FEV1/FVC >= 70%
- Treatment naïve patients

External Control Arm Generation
- 20,000 randomly sampled groups of 48 patients generated from filtered control data
- 1:1 treatment-control ratio
- Matching on 8 clinical variables at baseline
- Univariate and multivariate tests of similarity with control
- 408 randomly sampled groups accepted as control arms based on the baseline similarity tests
- Mean similarity p-value = 0.23 (SD = 0.05)

Efficacy Testing
- Follow-up time – 36 weeks
- AIR – mean FVC change +23 ml
- Control – mean FVC change -114.8ml

Results

Figure 5: FVC Change over 36 weeks in observed data

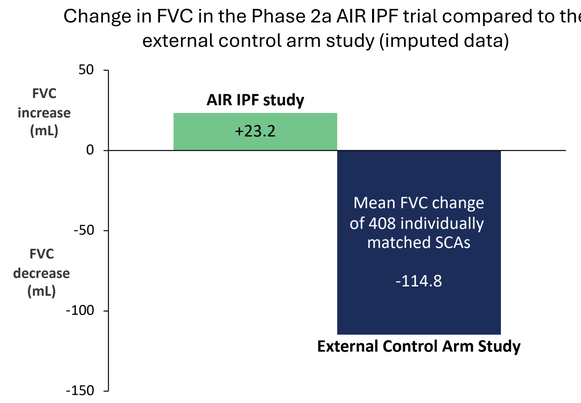


Note: n=48 patients with 2-week FVC data. Observed values, no imputation.
[#] Untreated: Expected average decline for untreated patients based on published placebo data[1,2].
*p<0.05, **p<0.01, ***p<0.001; t-test versus expected untreated decline corresponding to -180 mL/36 weeks.

[1]Noble et al. Eur Respir J. 2016 Jan; 47(1): 243–253
[2]Richeldi et al. Engl J Med 2014; 370:2071-2082

The trial enrolled 52 participants with a mean percent predicted FVC 75.5% (SD 13.7). In patients completing 36 weeks (n=28), FVC improved by 216 ml (90% CI + 37, +395) from baseline. Buloxibutid was well tolerated without serious adverse reactions.

Figure 6 – Change in FVC in AIR Compared to SCA



The mean decline in the 408 control arms was 114.8 ml over 36 weeks, consistent with placebo arm result from recent IPF trials. This compares to a 23.2 ml improvement with buloxibutid when imputing missing data in AIR using the mean decline in the SCA arms.

ASPIRE Phase2b Study in IPF – Currently recruiting

Screening	Buloxibutid (C21) 50 mg twice daily for 52 weeks; N=90 Buloxibutid (C21) 100 mg twice daily for 52 weeks; N=90 Placebo twice daily for 52 weeks; N=90	Follow-up

Conclusions

The data from AIR study provides the rationale for conducting a Phase 2b study in IPF patients. ASPIRE is a Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial Evaluating the Efficacy and Safety of 2 Doses of a new therapy Over 52 Weeks in People with Idiopathic Pulmonary Fibrosis.

- In the open-label AIR study, buloxibutid treatment was associated with an improvement in FVC.
- Working with Qureight, a matched synthetic control arm was generated from a contemporary database with a high degree of accuracy.
- Conservative imputation of missing data and a generation of synthetic placebo control arms support buloxibutid beneficial treatment effect.

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