Buloxibutid (C21), a Novel Angiotensin II Type 2 Receptor Agonist in the 36-week Phase 2a AIR Trial

Stabilized and Improved Lung Function in Individuals with Idiopathic Pulmonary Fibrosis (IPF)

Ganslandt, C.[1], Maher, T.M.[2], Molyneaux P.L.[3], Lindmark B.[1], Raud J.[1], Tornling, G.[1,4], Bengtsson, T.[1], Rosendahl, E.[1]

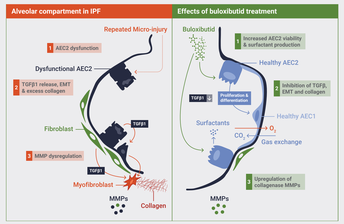
[1]Vicore Pharma, Stockholm, Sweden, [2]Keck School of Medicine of USC, Los Angeles, USA, [3]Imperial College London, United Kingdom, [4]Karolinska Institutet, Stockholm, Sweden

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and fatal interstitial lung disease. To date, no therapy has demonstrated the ability to reverse declining lung function, nor to reduce mortality, and available therapies are poorly tolerated.

Buloxibutid (C21) is an oral, selective angiotensin II type 2 (AT2) receptor agonist, driving an upstream pathway that improves alveolar epithelial type 2 cell function, triggers a cascade of anti-fibrotic activity, and resolves disease-associated vascular remodeling.

Buloxibutid is an oral, selective AT2R agonist with multiple beneficial effects on alveolar epithelial type 2 cells (AEC2)



Objectives

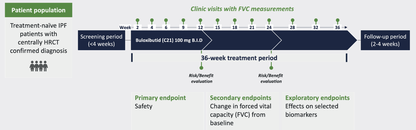
To investigate the safety and efficacy of oral buloxibutid 100 mg twice daily for up to 36 weeks in participants with IPF.

Methods

- AIR (NCT04533022) is a multi-center, open-label, single-arm, 36 week phase 2 trial
- Participants were enrolled with centrally confirmed IPF (UIP or probable UIP) and not currently receiving anti-fibrotic therapy
- Oral buloxibutid 100 mg twice daily was given for 24 weeks, with an optional extension to 36 weeks
- A benefit-risk evaluation for continued treatment was conducted every 12 weeks
- Spirometry was done at each site visit and centrally overread
- **Safety endpoints** included treatment emergent adverse events, serious adverse events and withdrawals due to adverse events
- The primary **efficacy endpoint** was change from baseline in FVC; analyzed at week 12, 24 and 36
- Analyses of FVC were performed using a t-test with the lower confidence interval for a 24-week change set at -120 mL (expected untreated decline[1,2])
- **Exploratory endpoints** included key biomarkers of fibrosis and fibrolytic activity

AIR - an open-label, international, phase 2a trial of oral buloxibutid 100 mg BID for up to 36 weeks in treatment-naïve IPF patients

Trial design



* iDMC monitoring of safety data (4 regular reviews)

Results

Patient disposition

- 52 participants were enrolled between 09 Dec 2020 and 22 Jun 2023
- 28 participants completed the 36-week visit



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

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

Baseline demographic and disease characteristics

		Buloxibutid 100 mg BID, N=52
Age (years); mean (SD)		67.3 (9.38)
Gender	Male; n (%)	40 (77%)
	Female; n (%)	12 (23%)
Race	Asian; n (%)	38 (73%)
	White; n (%)	14 (27%)
Weight (kg); mean (SD)		64.6 (14.18)
Body mass index (kg/m2); mean (SD)		24.6 (4.12)
Time since IPF diagnosis (years); mean (SD)		1.0 (1.20)
FVC	Mean - mL (SD)	2387 (667)
	Median - mL	2300
	% predicted; mean (SD)	75.5 (13.66)
FEV1/FVC ratio; mean (SD)		0.80 (0.067)
Oxygen saturation (%); mean (SD)		95.3 (2.40)
HRCT pattern (central read)	Typical UIP	20 (39%)
	Probable UIP	32 (61%)
Previous use of anti-fibrotics		0 (0%)

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

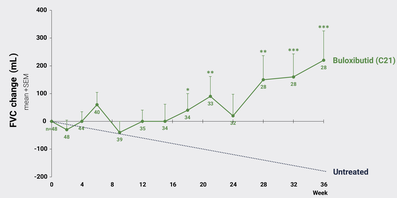
Most common TEAEs - any causality	Buloxibutid 100 mg BID, N=52, n (%)
Hair loss	10 (19.2)
Rash	4 (7.7)
Cough	4 (7.7)
Gastro-esophageal reflux disease	4 (7.7)
Blood creatinine increased	4 (7.7)
Pyrexia	4 (7.7)

* SAEs: Angina pectoris, COVID-19, acute IPF exacerbation, oral squamous cell carcinoma, pneumonitis (complicated with type 2 diabetes mellitus, kidney infection, sepsis, cardiac failure)
† Fatal SAEs: COVID-19, pneumonitis (complicated with type 2 diabetes mellitus, kidney infection, sepsis, cardiac failure)

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

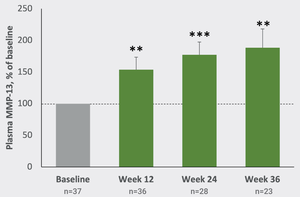
Efficacy

Buloxibutid stabilizes and improves FVC over 36 weeks



Note: n=48 patients with 2-week data. Observed values, no imputation.
*p<0.05, ** p<0.01, ***p<0.001 versus fixed change of -120 mL/24 weeks applied to each week (untreated).
Untreated: Expected average decline for untreated patients based on published placebo data[1,2].

Buloxibutid increases collagenase MMP-13 in plasma



** p<0.01, ***p<0.001 versus baseline.

Discussion

Buloxibutid was safe and well tolerated for the full 36-week duration of the trial. The only adverse effect identified was mild-to-moderate reversible hair loss, experienced by less than 20% of patients. Only one patient discontinued treatment due to this side effect. The early drop-out rate was higher than expected, to a large extent explained by the COVID-19 pandemic and frequent trial visits biweekly for the first 12 weeks). Most patients experienced an increase in lung function from baseline at the conclusion of the 36-week study. Observed effects on biomarkers are supportive of the proposed tissue repair mechanism of action of buloxibutid.

Conclusions

- Lung function was improved at week 36 with a significant difference to expected decline of untreated IPF
- Observed effects on key biomarkers are consistent with the efficacy findings and proposed mechanism of action
- The safety profile shows excellent gastrointestinal tolerability and no treatment related serious adverse events
- These results warrant further investigation in a phase 2b setting, which is being planned as a 52-week, double-blind, randomized, placebo-controlled trial

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

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