VICORE PHARMA

Final Phase 2a AIR Data for Buloxibutid in IPF

Webinar discussing the late-breaking oral presentation at ATS 2024

May 22nd, 2024

Today's speakers

Ahmed Mousa

Chief Executive Officer

Bertil Lindmark

Chief Medical Officer

Prof. Toby Maher

Keck School of Medicine at University of Southern California

Moderator

Megan Richards

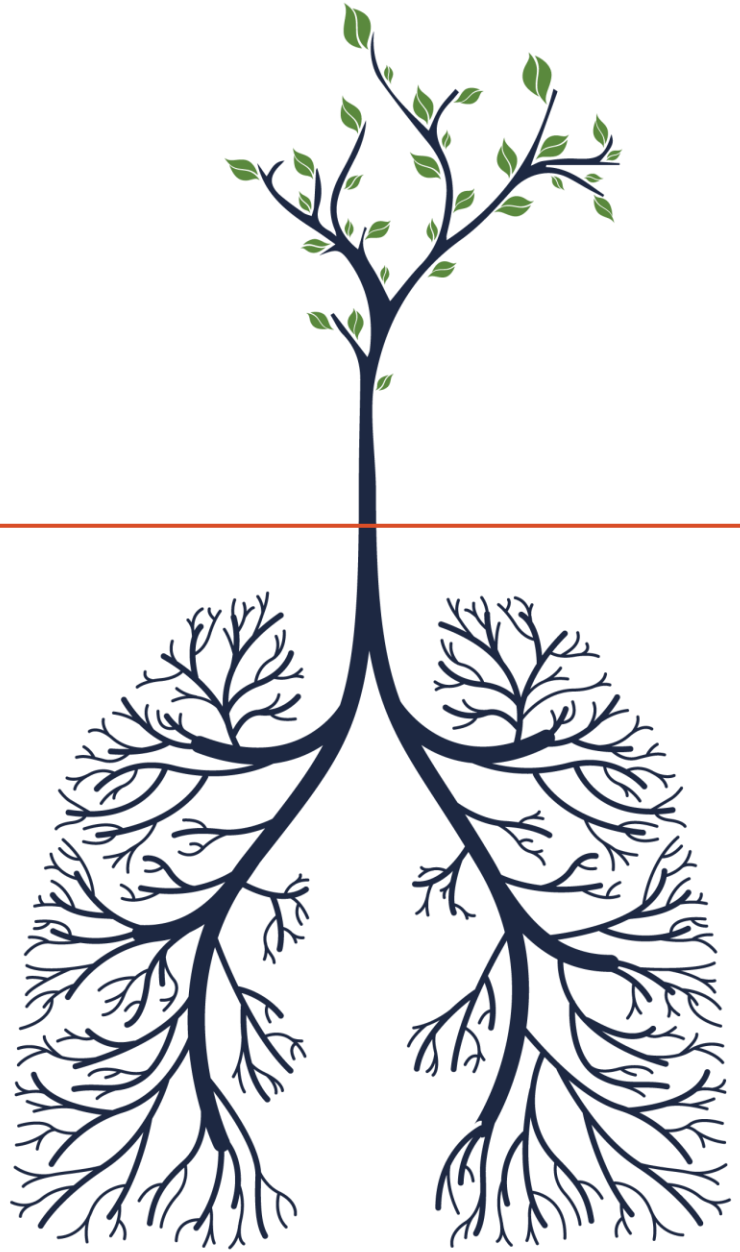
VP of IR, Communications, & Portfolio Strategy

Agenda

Welcome and rationale for buloxibutid in IPF	**Ahmed Mousa**
Final phase 2a AIR trial data with buloxibutid in IPF *Buloxibutid, 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)*	**Professor Maher**
AIR data context and deep dive	**Bertil Lindmark**
Putting it together and the phase 2b ASPIRE trial	**Ahmed Mousa**
Q&A session	

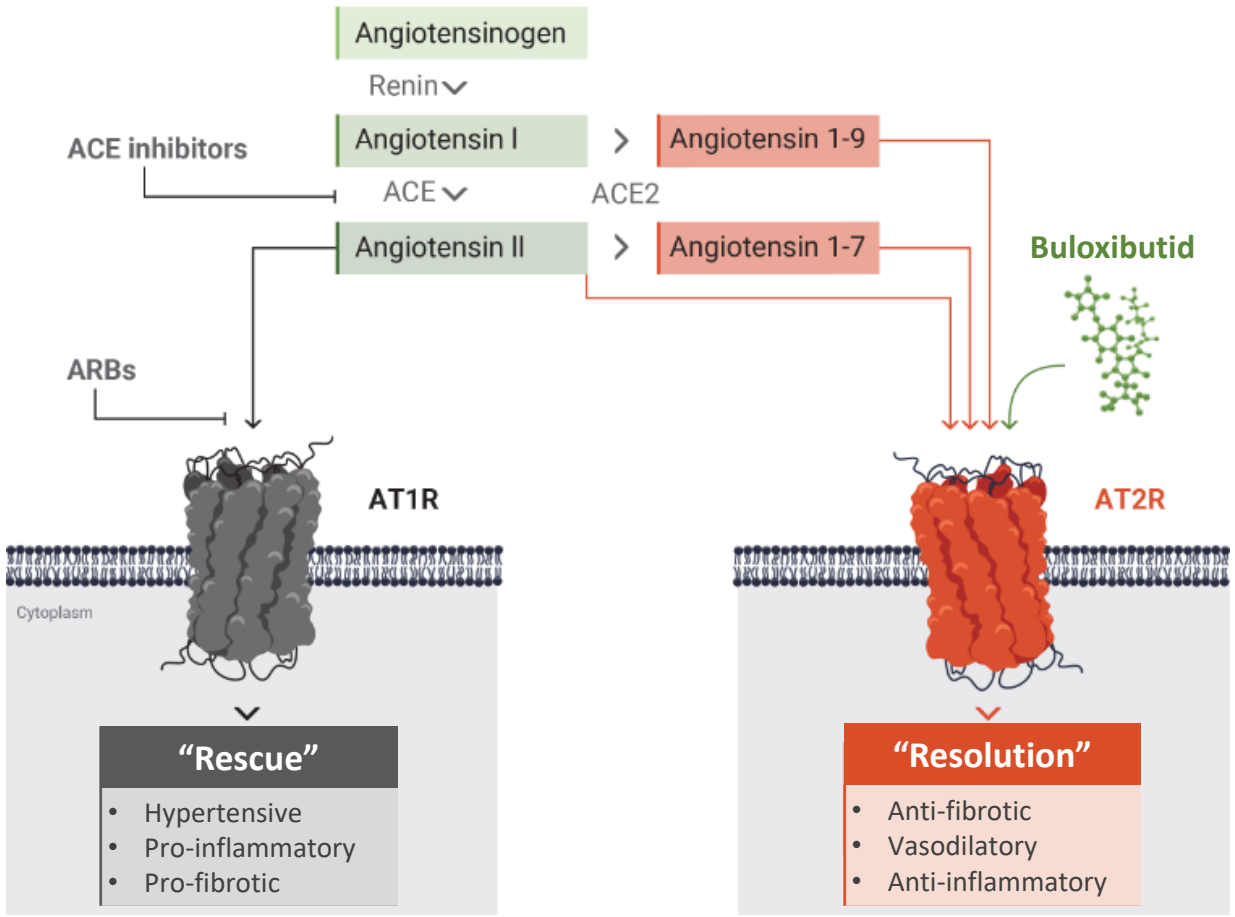
Rationale for buloxibutid in IPF

Ahmed Mousa
Chief Executive Officer



vicore pharma

Angiotensin II type 2 receptor (AT2R) agonism is an upstream intervention driving tissue repair

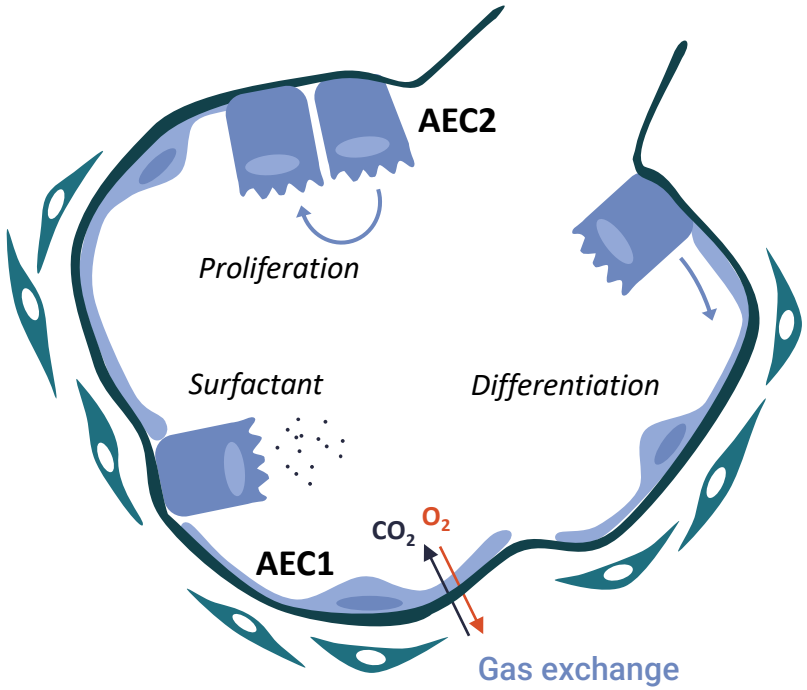


- AT2R constitutively expressed in the lung, primarily on alveolar epithelial type 2 cells (AEC2) – the "alveolar repair cell"
- AT2R activates tissue protective mechanisms via AEC2s, including anti-fibrotic effects
- Buloxibutid is an oral, selective AT2R agonist

The healthy alveolus and function of alveolar epithelial cells type 1 and 2

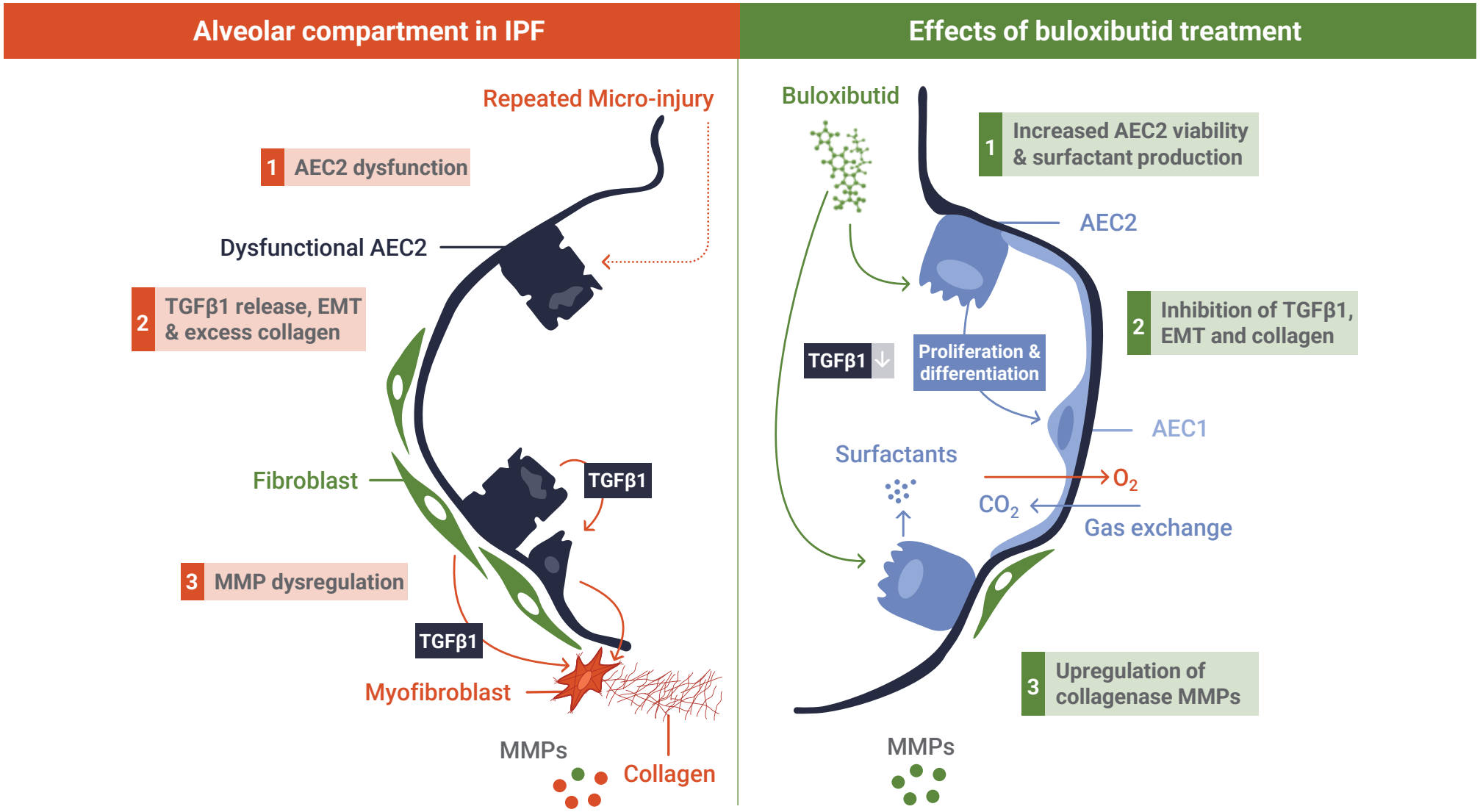
- AEC2 is a progenitor cell that is critical for alveolar integrity and function:
  - Proliferates to form new AEC2
  - Differentiates to AEC1 that need to be replaced
  - Produces surfactant to maintain alveolar integrity
- AEC1 is the predominant alveolar cell type and is responsible for gas exchange

Healthy alveolus



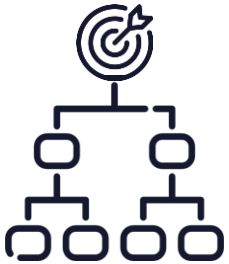
AEC – Alveolar Epithelial Cell

Buloxibutid is an oral, selective AT2R agonist that drives tissue repair via AEC2 precursor epithelial cells



EMT = Epithelial–mesenchymal transition; MMPs = Matrix metalloproteinases

Buloxibutid is positioned to transform the IPF landscape



Upstream MoA with strong preclinical data

- AT2 receptor expressed on alveolar progenitor cell (AEC2)
- Upstream MoA drives antifibrosis, surfactant production and collagenase expression

Exceptional clinical data in the phase 2a AIR trial

- Mean FVC change from baseline of +216 ml at 36 weeks
- All subgroups above baseline
- Biomarker data highly supportive of suggested MoA

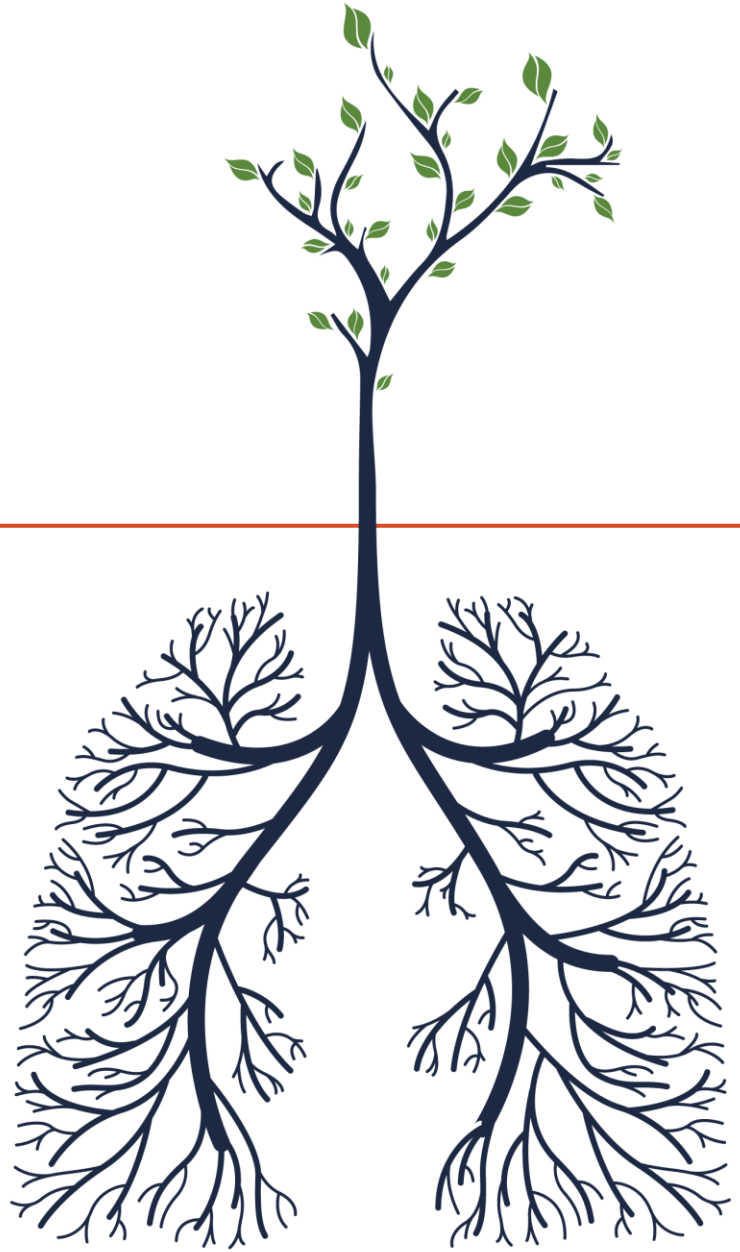
Phase 2b ASPIRE: confirming the clinical activity in a randomized, placebo-controlled trial

- 52-week treatment
- N=270 (90 per arm)
- IPF patients on stable nintedanib/SoC or not on SoC
- Global footprint

Buloxibutid, 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)

Prof. Toby Maher
Keck School of Medicine at University of Southern California

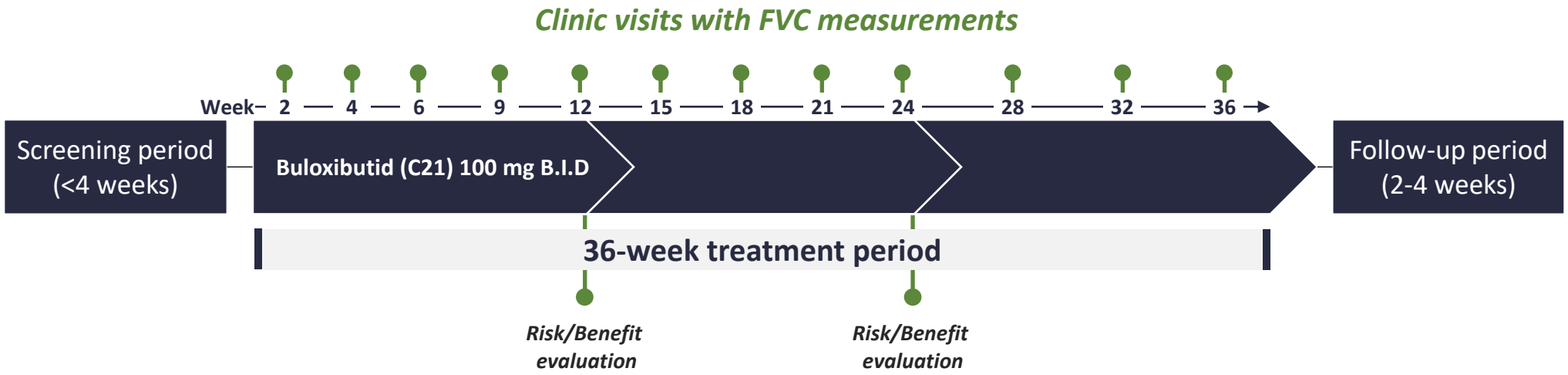


vicore pharma

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

Patient population

Treatment-naïve IPF patients with centrally HRCT confirmed diagnosis



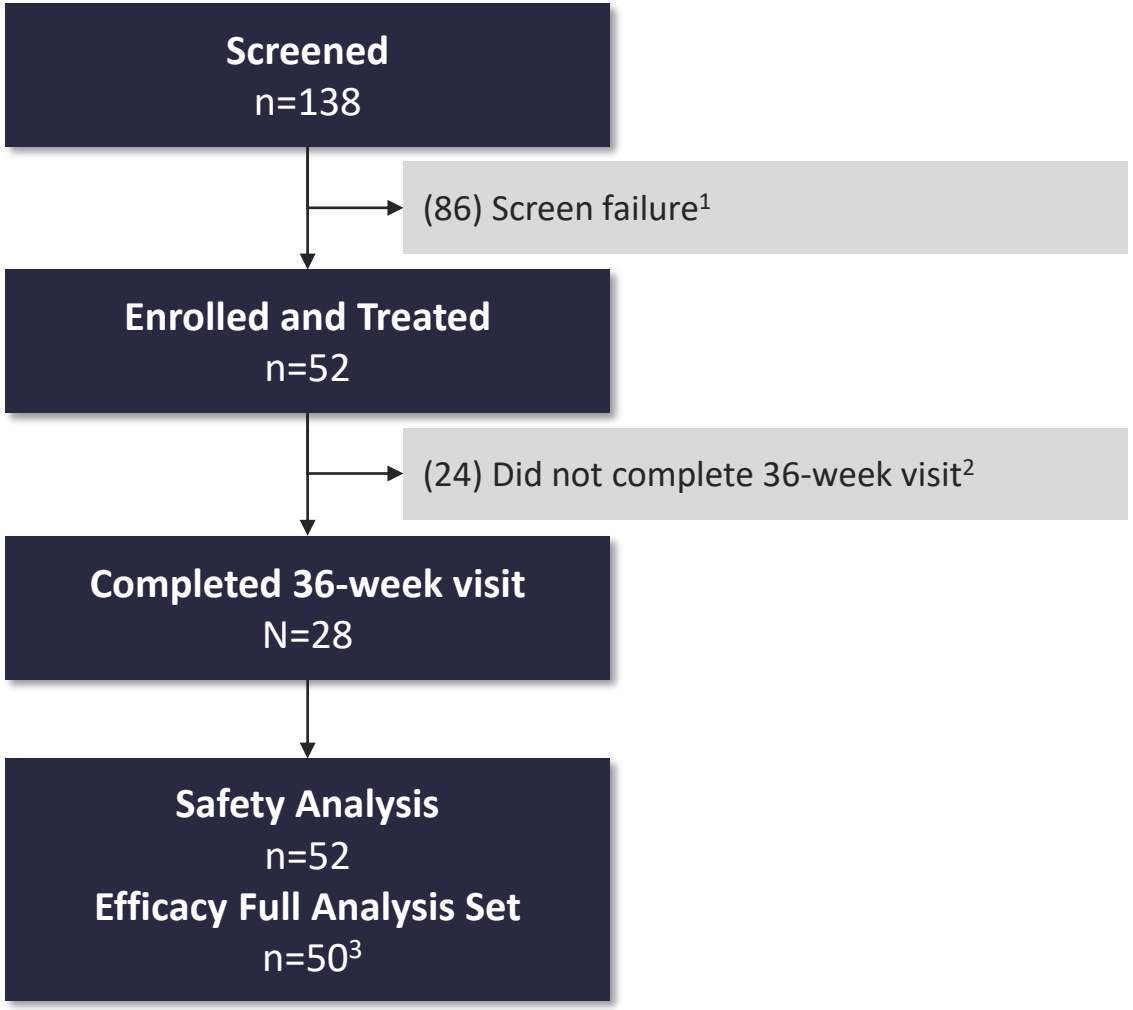
Primary endpoint
Safety and tolerability

Secondary endpoints
Change in forced vital capacity (FVC) from baseline

Exploratory endpoints
Effects on selected biomarkers

vicore pharma

Disposition of patients



- 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*

Demographic and baseline disease characteristics

Baseline demographics

Characteristic		Buloxibutid 100 mg BID N=52
Age (years); mean (SD)		67.3 (9.38)
Gender	Male; n (%) Female; n (%)	40 (77%) 12 (23%)
Race	Asian; n (%) White; n (%)	38 (73%) 14 (27%)
Weight (kg); mean (SD)		64.6 (14.18)
Body mass index (kg/m^2); mean (SD)		24.6 (4.12)

Baseline disease characteristics

Characteristic		Buloxibutid 100 mg BID N=52
Time since IPF diagnosis (years); mean (SD)		1.0 (1.20)
FVC	Mean - mL (SD) Median - mL % predicted; mean (SD)	2387 (667) 2300 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; n (%) Probable UIP; n (%)	20 (39%) 32 (61%)
Previous use of anti-fibrotics		0 (0%)

vicore pharma

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

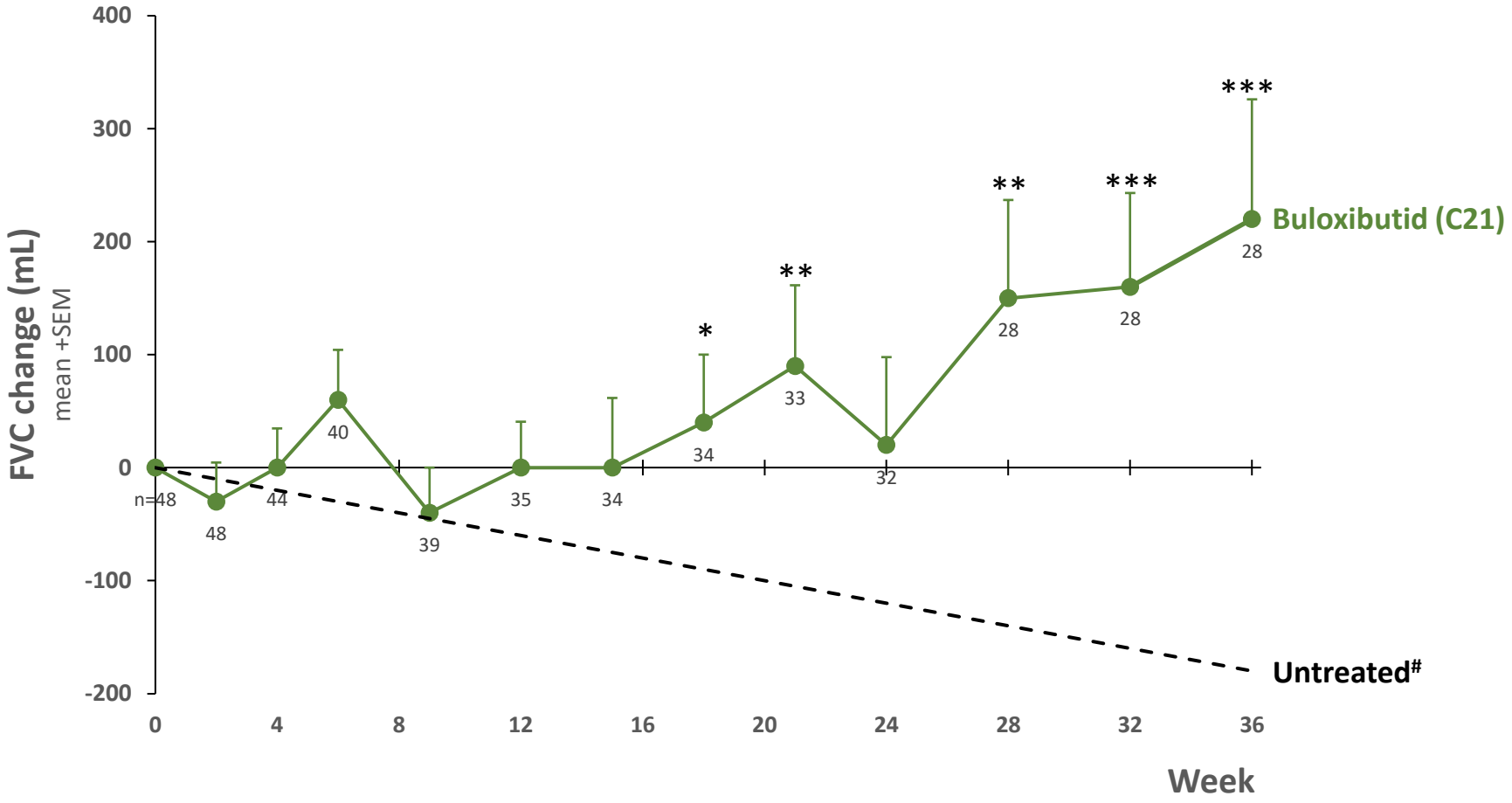
Most common TEAEs - any causality	Buloxibutid 100 mg BID N=52 n (%)
Hair loss	10 (19.2)
Rash	4 (7.7)
Cough	4 (7.7)
Gastro-esophageal reflux disease	4 (7.7)
Blood creatinine increased	4 (7.7)
Pyrexia	4 (7.7)

- **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**

*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)

vicore pharma

Stabilization and improvement of FVC over 36 weeks



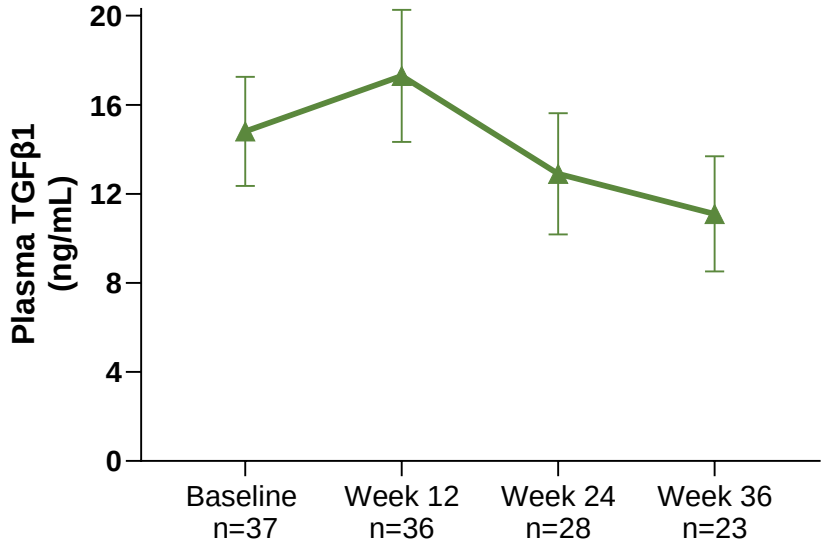
Note: n=48 patients with 2-week FVC data. Observed values, no imputation.
Untreated: Expected average decline for untreated patients based on published placebo data[1,2].
*p<0.05, **p<0.01, ***p<0.001; t-test versus expected untreated decline corresponding to -120 mL/24 weeks

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

vicore pharma

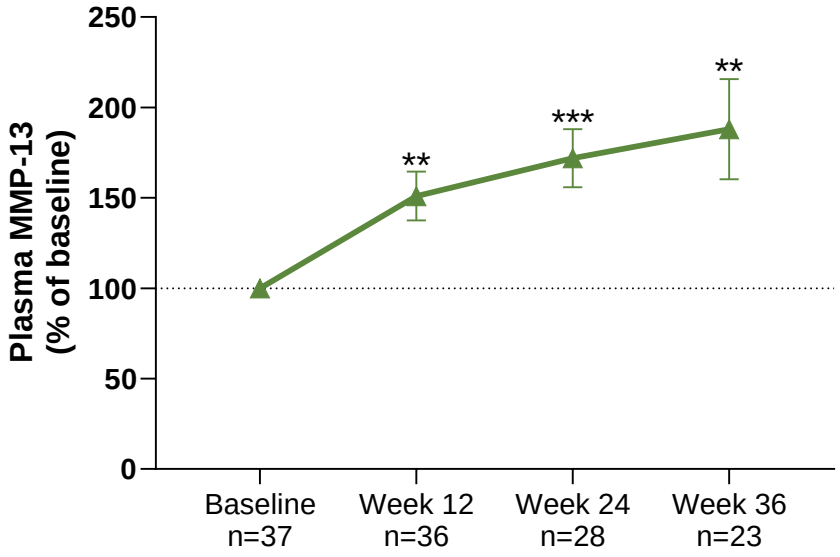
Buloxibutid drives a trend of decreased TGFβ1 and increases collagenase MMP-13

Plasma TGFβ1



TGFβ1 is a key fibrotic driver in IPF; reduced TGFβ1 is consistent with buloxibutid's mechanism of action and translational data

Plasma MMP-13



MMP-13 is an antifibrotic collagenase that plays a positive role in fibrotic resolution

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

Buloxibutid in idiopathic pulmonary fibrosis

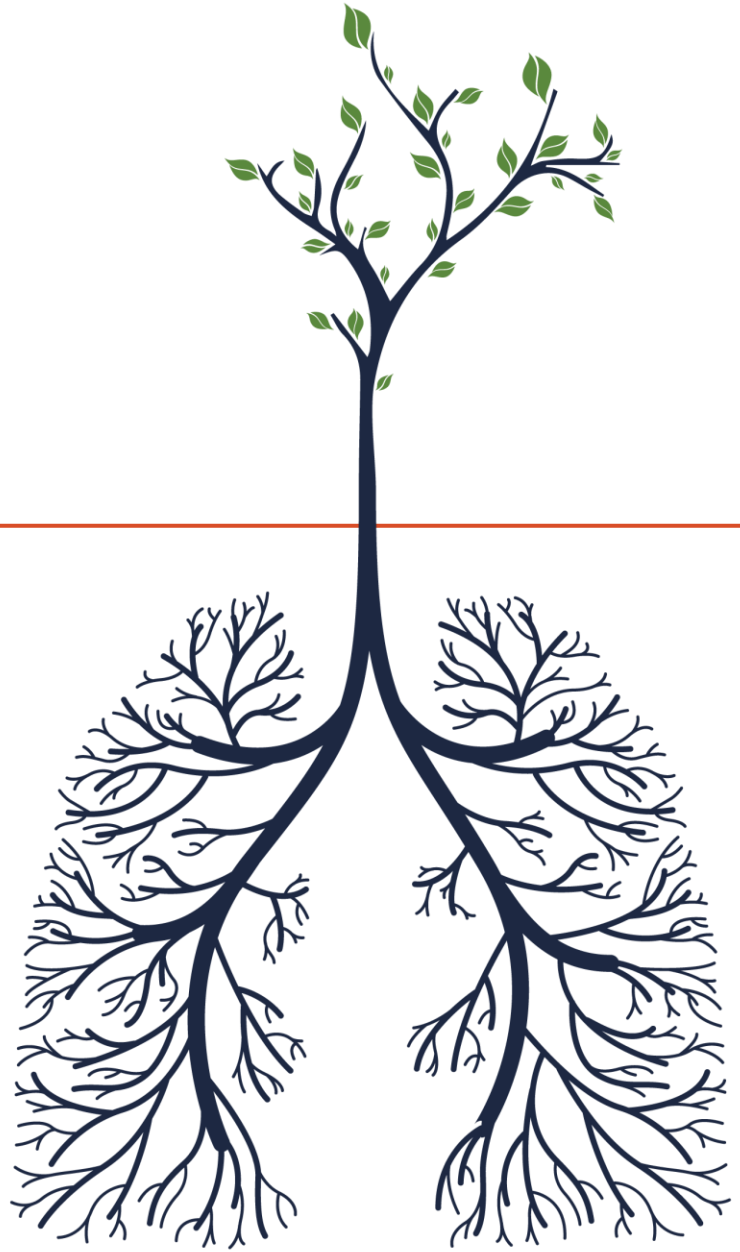
Buloxibutid is an upstream intervention with a novel mechanism of action expected to drive tissue repair in IPF

The safety profile shows excellent gastrointestinal tolerability and no treatment related serious adverse events

Lung function stabilized and improved over 36 weeks with significant treatment effect over untreated decline, supported by key biomarkers

AIR data context and deep dive

Bertil Lindmark
Chief Medical Officer



vicore pharma

Baseline patient characteristics in line with other IPF trials

Key Characteristics

		AIR (N=52)	INPULSIS 1&2 (N=1,061)[1]
Age (years) - Mean (SD)		**67 (9)**	67 (8)
Gender	Males	**77%**	80%
	Females	**23%**	20%
Ethnicity	White	**27%**	57%
	Asian	**73%**	30%
BMI (kg/m^2) – Mean (SD)		**24.6 (4.1)**	28 (4.6)
FVC % predicted - Mean (SD)		**75.5 (14)**	79.7 (17)
% SoC	Pirfenidone	**0%**	0%
	Nintedanib	**0%**	0%

In line with other trials.

Enrolled study population has disease progression comparable to global IPF study populations.

In line with other trials.

As with the INPULSIS trials, AIR patients were treatment-naïve.

1) INPULSIS 1&2 were the phase 3 studies that led to the approval of nintedanib; Richeldi et al. N Engl J Med 2014; 370:2071-82

Treatment emergent adverse events: buloxibutid shows better tolerability than SoC

	Ph3 INPULSIS-1 *52-week treatment*[1]		Ph2a AIR *36-week treatment*
	Nintedanib n=309	**Placebo** n=204	**Buloxibutid** n=52
Any AE	96%	89%	71%
Common AEs (Non-exhaustive)			
Diarrhea	62%	19%	6%
Nausea	23%	6%	4%
Acute exacerbation of IPF	10%	10%	6%
Cough	15%	13%	8%
Vomiting	13%	2%	2%
COVID-19	n/a	n/a	6%
Hair loss[2]	n/a	n/a	19%
Fatal AE	4%	5%	4%
Severe AE	26%	18%	6%
Serious AE	31%	27%	10%

Good GI side effect profile

Low rate of exacerbations and cough worsening

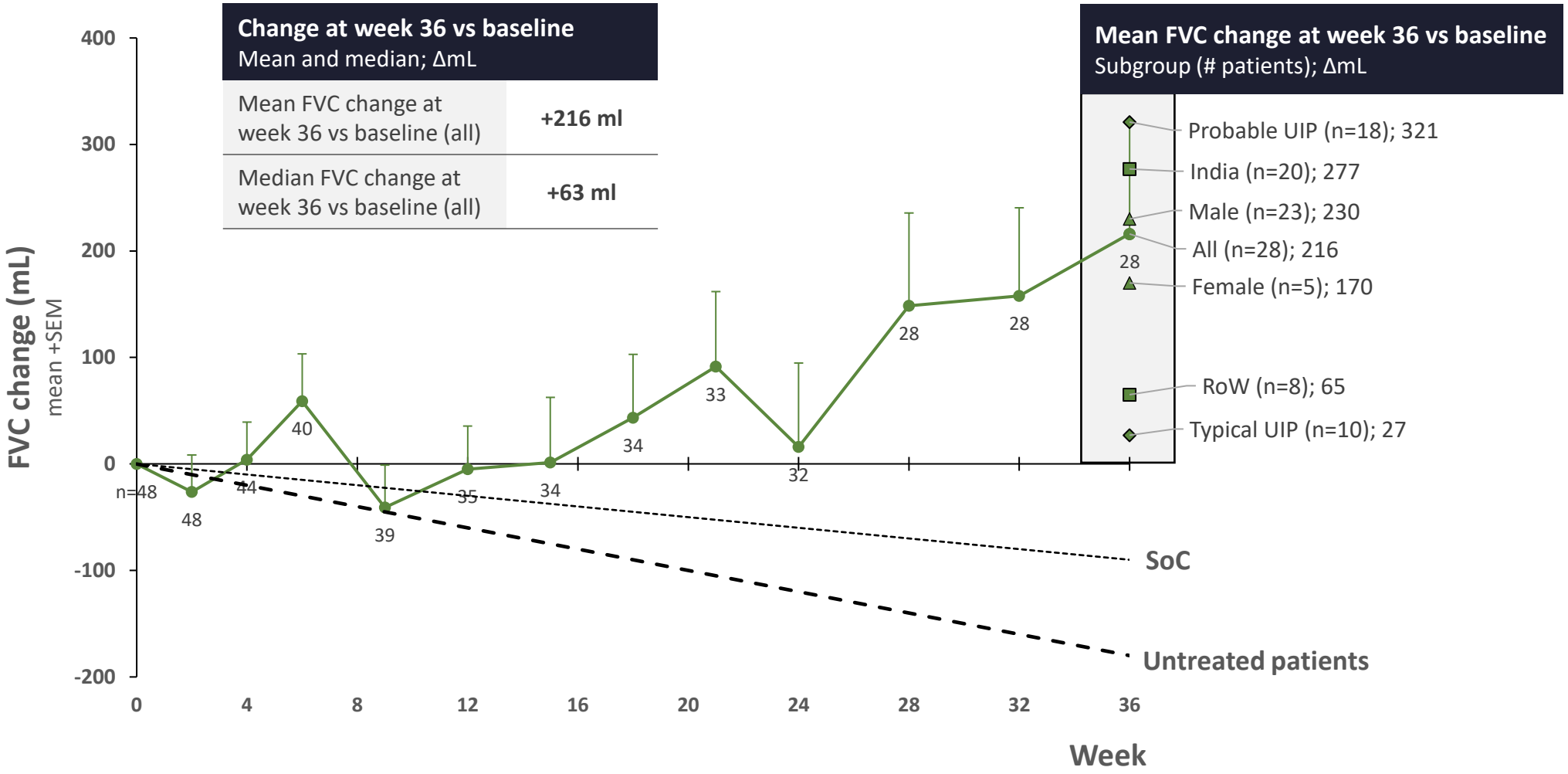
No serious, severe, or fatal AEs related to buloxibutid

Buloxibutid has a favorable tolerability profile allowing it to be combined with other therapies for IPF

Note: Rash, gastroesophageal reflux disease, elevated creatinine, and pyrexia were also reported at 8% in AIR trial

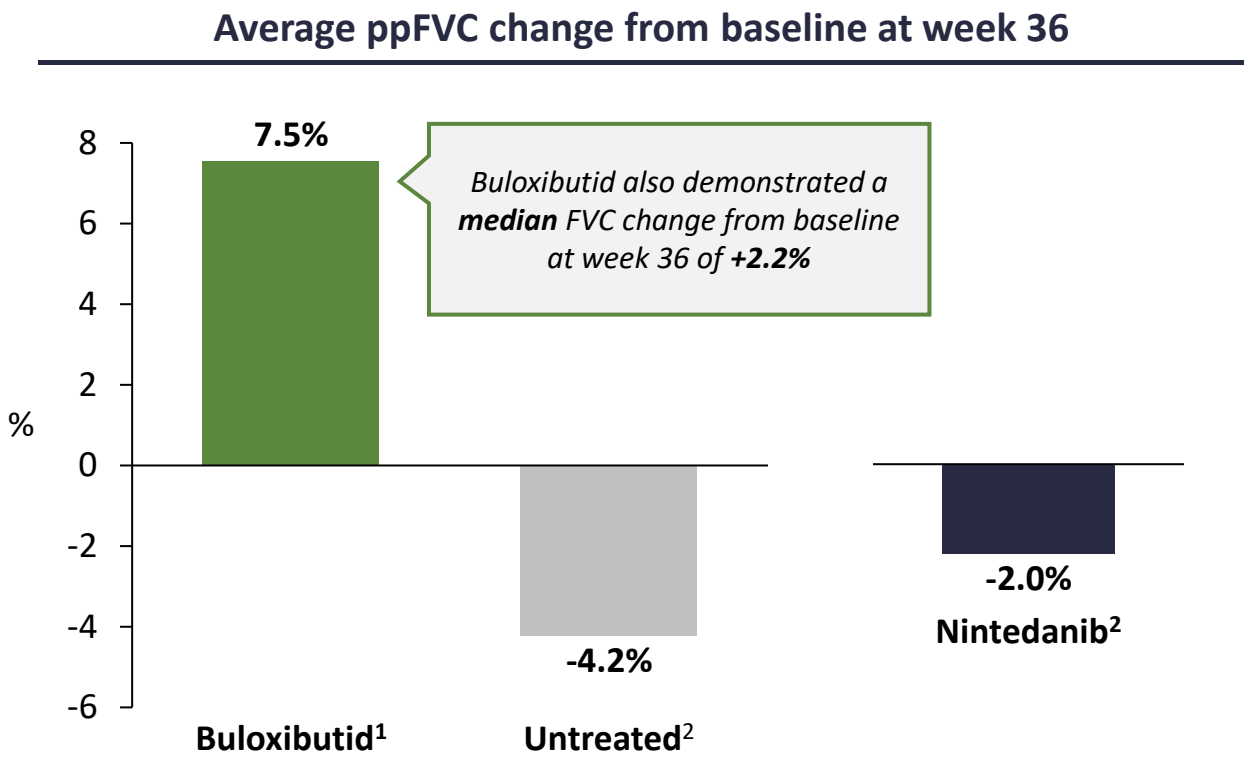
(1) Richeldi et al. N Engl J Med 2014; 370:2071-82; (2) Hair loss was mild to moderate and reversible. One patient discontinued treatment due to hair loss.

All subgroups show FVC stabilization and increase over baseline at 36 weeks



Note: Probable UIP and Typical UIP according to HRCT categorization at baseline.

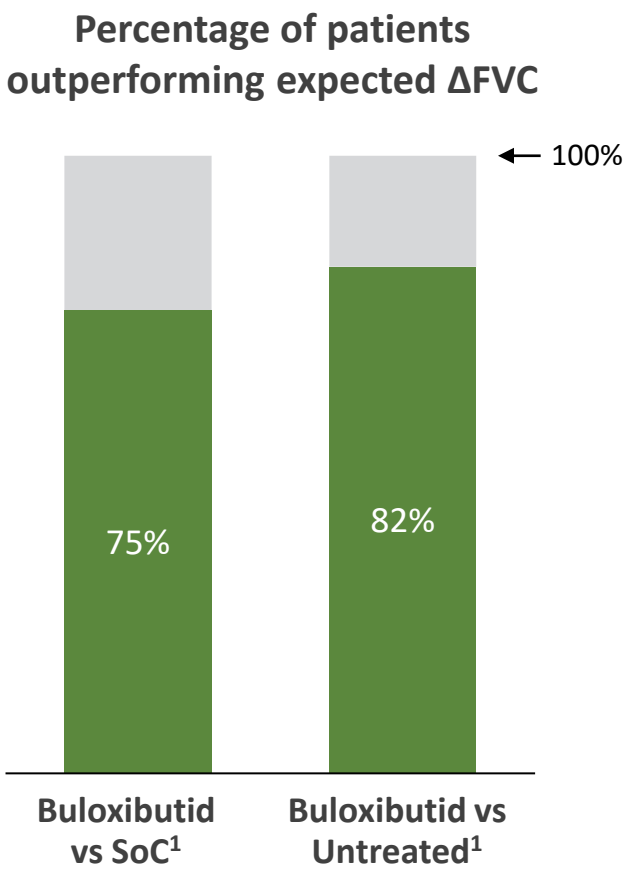
Increase in percent predicted FVC consistent with increase in absolute FVC



7.5% increase in percent predicted FVC at 36 weeks

1) Average ppFVC at 36 weeks (n=28)
2) 36 week estimated ppFVC for nintedanib and placebo; INPULSIS trial (Richeldi et al. N Engl J Med 2014; 370:2071-82)

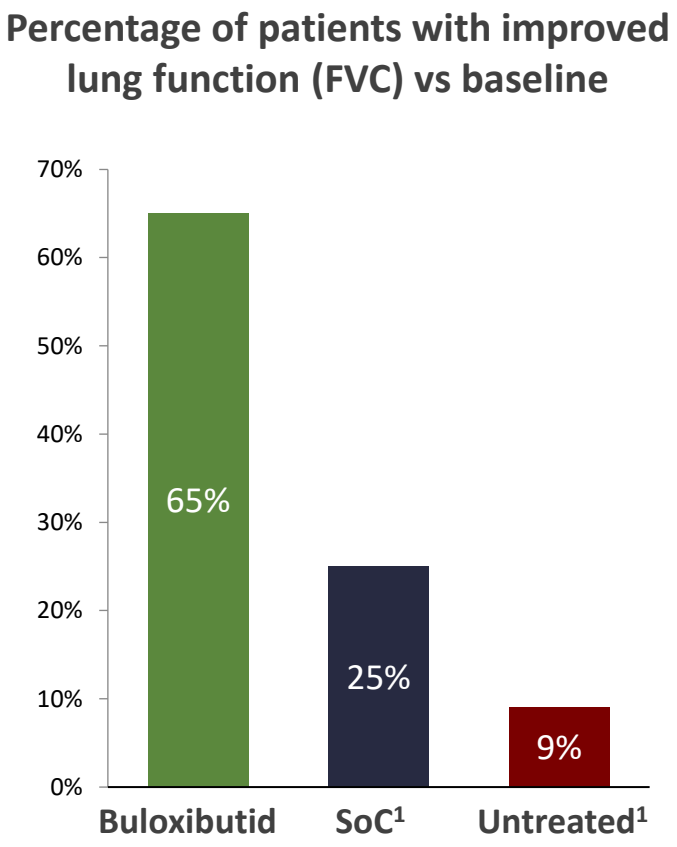
Putting it in context: buloxibutid vs historical standard of care and untreated decline



Buloxibutid outperforms expected change in FVC of untreated patients and those treated with current standard of care at 36 weeks

1) Based on historical data (Richeldi et al. N Engl J Med 2014; 370:2071-82)

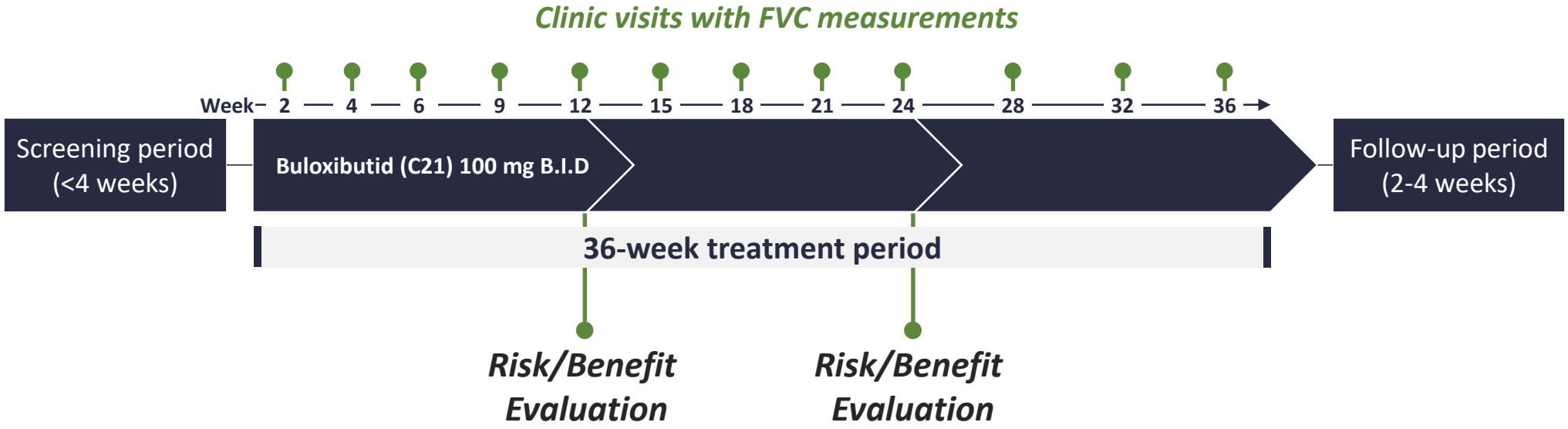
Putting it in context: buloxibutid vs historical standard of care and untreated decline



Most patients treated with buloxibutid experience improved lung function at 36 weeks, outperforming historical SoC and untreated patients

1) Based on historical data. Flaherty, et al., 2018; Note: 25% of patients treated with nintedanib over 52 weeks showed improvement or no decline in FVC in the INPULSIS trials, and for untreated patients the number was 9%.

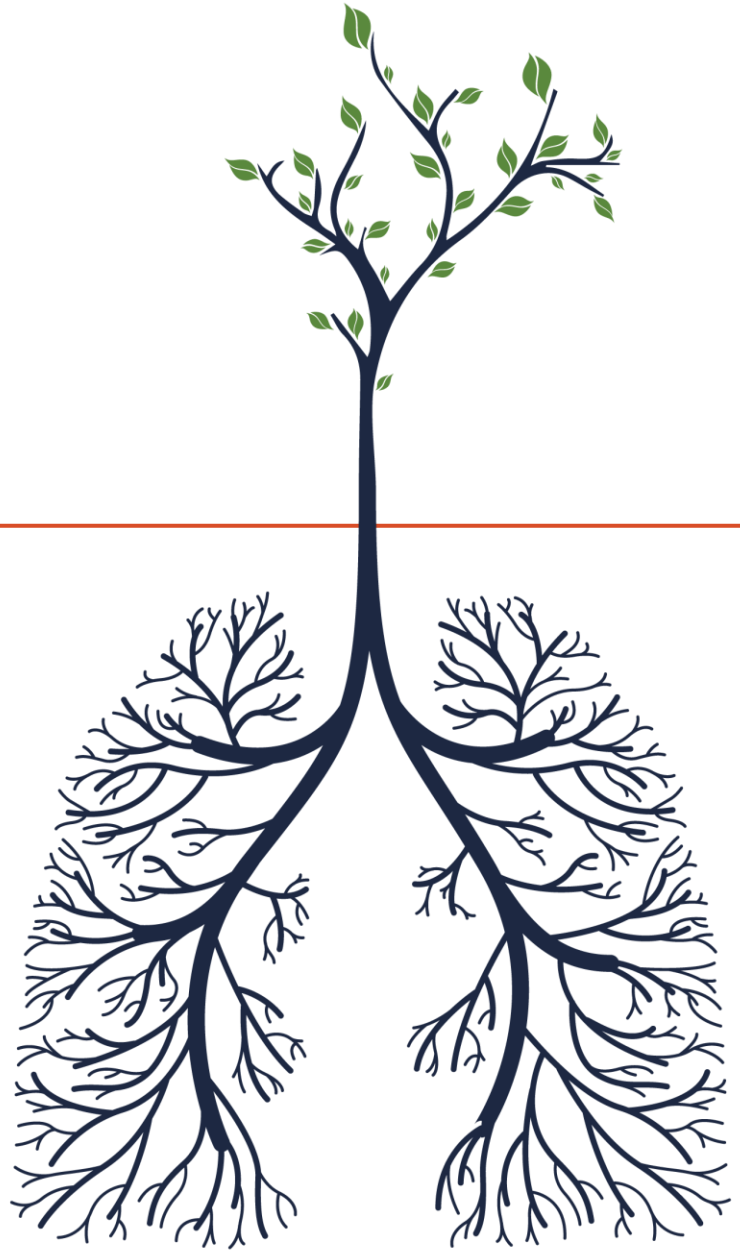
Physicians overwhelmingly determined to keep patients on therapy rather than move to SoC



- At weeks 12 and 24, each investigator completed a medical evaluation to assess the benefit/risk for the patient to **continue in the trial without the use of standard of care therapy** for IPF
- At each of the two timepoints, **97% of patients had a positive benefit/risk and continued treatment**

Putting it together & the phase 2b ASPIRE trial

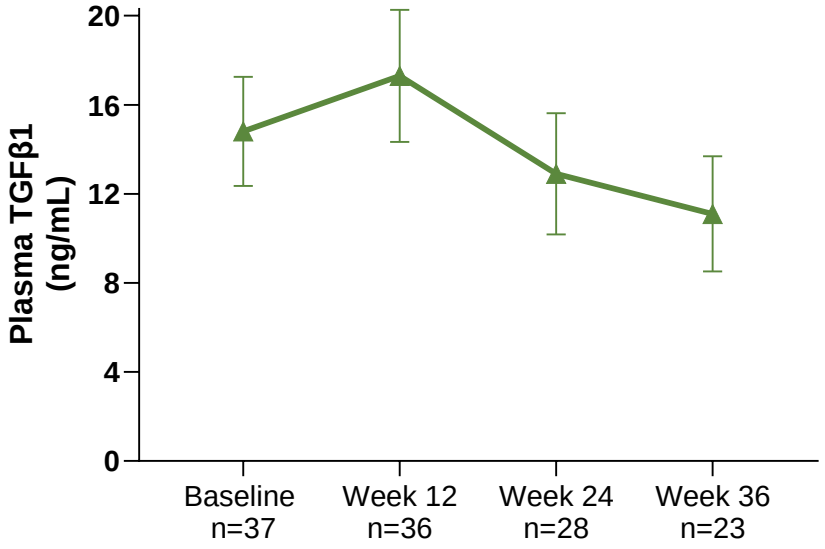
Ahmed Mousa
Chief Executive Officer



vicore pharma

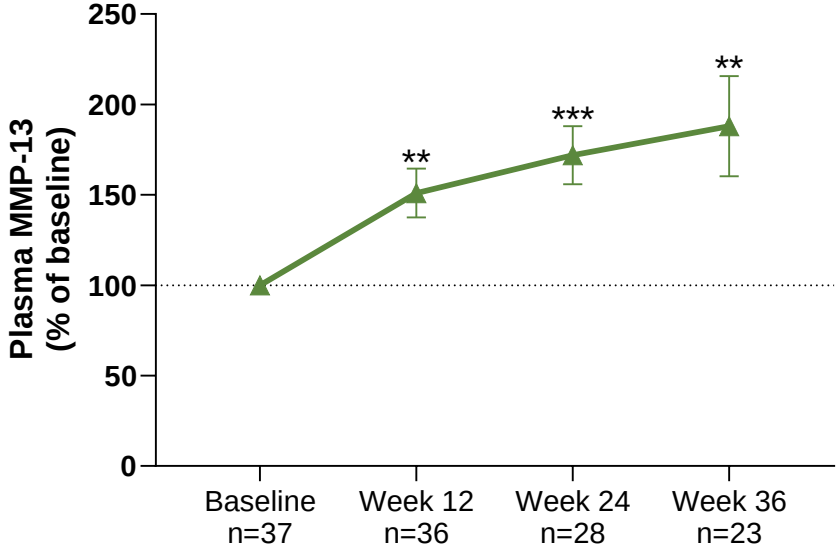
Buloxibutid drives a trend of decreased TGFβ1 and increases collagenase MMP-13

Plasma TGFβ1



TGFβ1 is a key fibrotic driver in IPF; reduced TGFβ1 is consistent with buloxibutid's mechanism of action and translational data

Plasma MMP-13



MMP-13 is an antifibrotic collagenase that plays a key role in fibrotic resolution

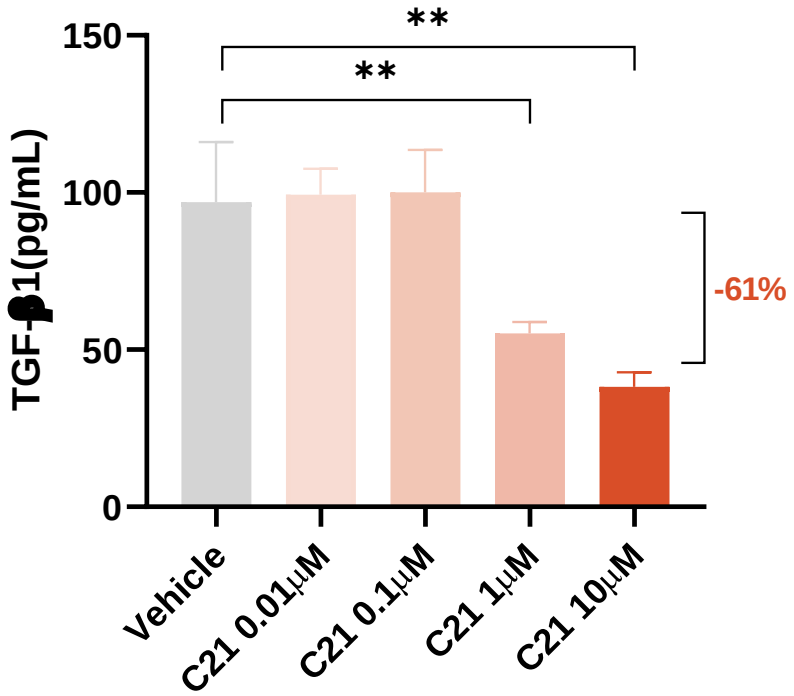
Note: data shown as mean ±SEM
** p<0.01, ***p<0.001 paired t-test vs baseline

The reduction in plasma TGFβ1 seen clinically is supported by preclinical data showing decrease of TGFβ1 in human lung slices

TGFβ1 is a potent fibrogenic cytokine

- Stimulates **extracellular matrix** formation
- **Drives differentiation of AEC2s to fibroblasts and myofibroblasts** via epithelial-to-mesenchymal transition and promotes fibroblast myofibroblast transition
- Drives imbalance of **MMPs** (matrix metalloproteases) associated with disease progression

TGFβ1 protein levels in PCLuS[1]



Consistent with clinical biomarker findings, a dose-dependent reduction of TGFβ1 is observed in human lung slices treated with buloxibutid

(1) Data represent averages +/- SEM of of 5 separate tissue slices at each concentration, sampled after 144h exposure to C21 or vehicle. PCLuS: precision cut human lung slices
Source: Vicore data on file

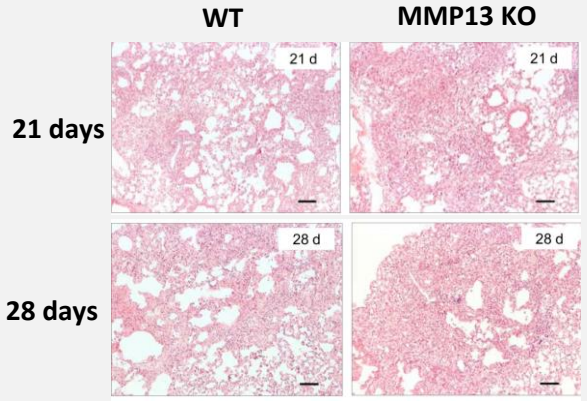
MMP13 demonstrates antifibrotic activity and is crucial for lung repair in IPF

MMP dysregulation contributes to IPF pathogenesis

- MMP13 is an enzyme able to **cleave fibrillar collagens** and plays a significant role in **ECM remodeling**
- In mouse models, MMP13 deficiency has been shown to[1,2]:
  1. Decrease collagenolytic activity
  2. Promote lung fibrosis
  3. Attenuate fibrosis resolution

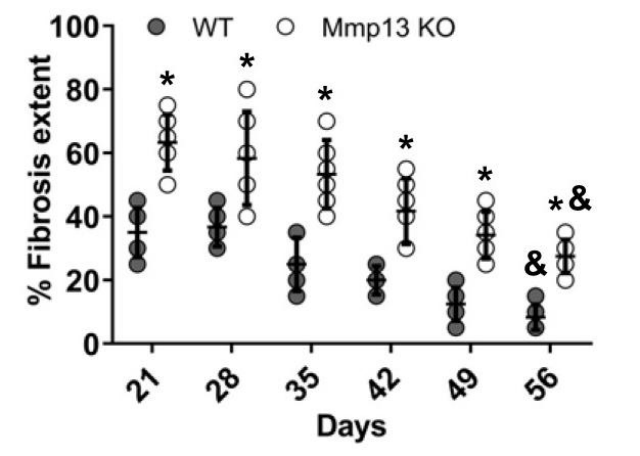
Bleomycin-Challenged MMP13 -/- vs. WT Mice

Cabrera et al., 2019



MMP13-deficient mice exhibited more extensive and severe lung fibrosis post-bleomycin exposure

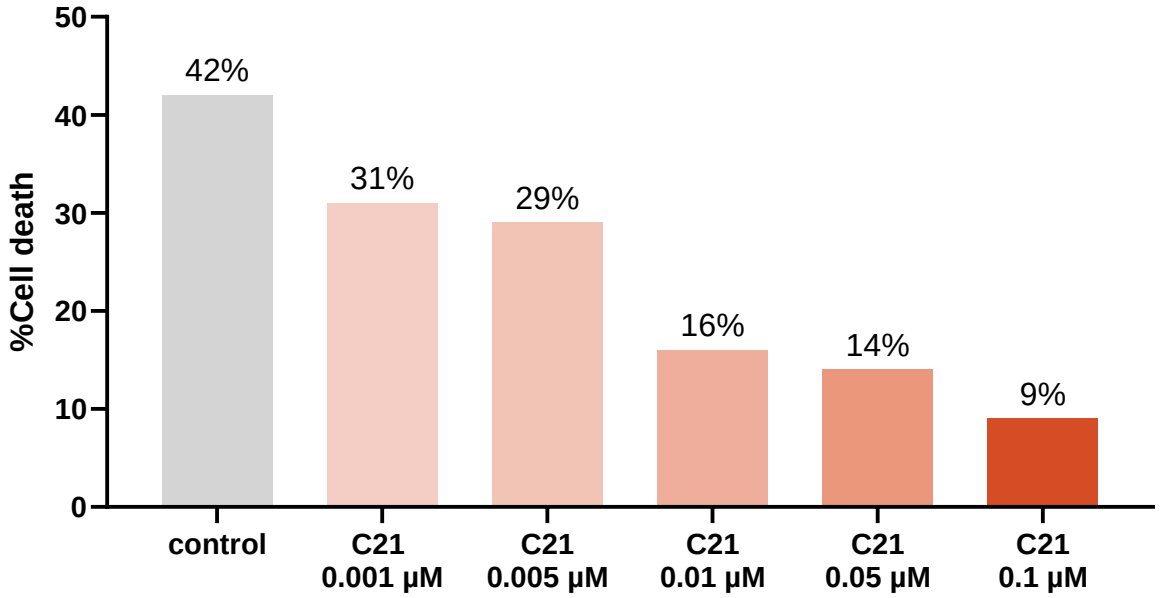
The percentage of damaged lung area was significantly higher in MMP-13 KO mice vs. WT



ECM = Extracellular Matrix; MMP = Matrix Metalloproteases
Sources: (1) Cabrera et al., 2019; (2) Nkyimbeng et al., 2013

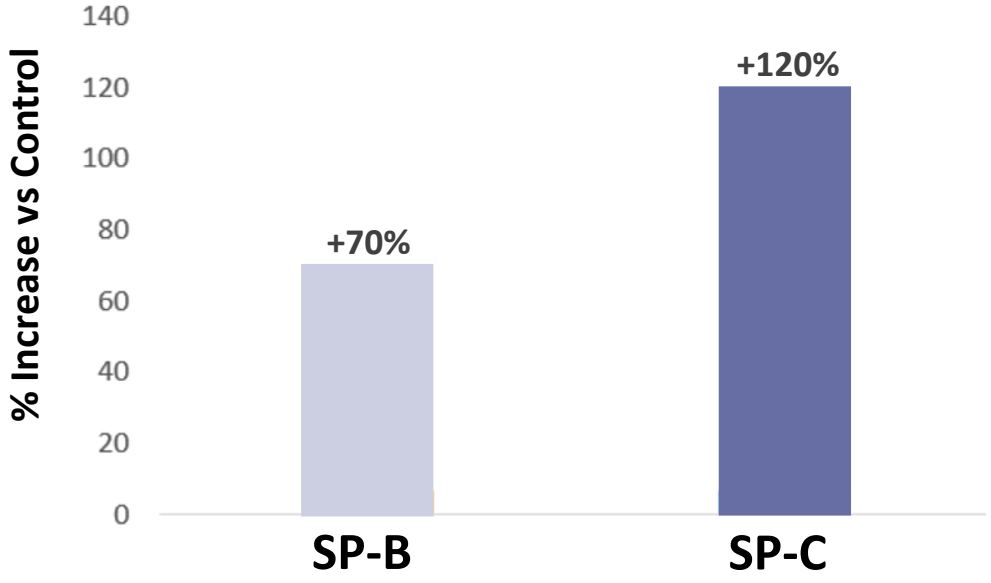
Buloxibutid protects AEC2s and drives increased surfactant production

Buloxibutid (C21) protects AEC2 cells against apoptosis[1]



- Cultured A549 cells (human AEC2 cell line)
- Bleomycin (10µg/ml) induced apoptosis

Surfactant protein expression increased by buloxibutid in ex vivo human IPF precision cut lung slices[2]



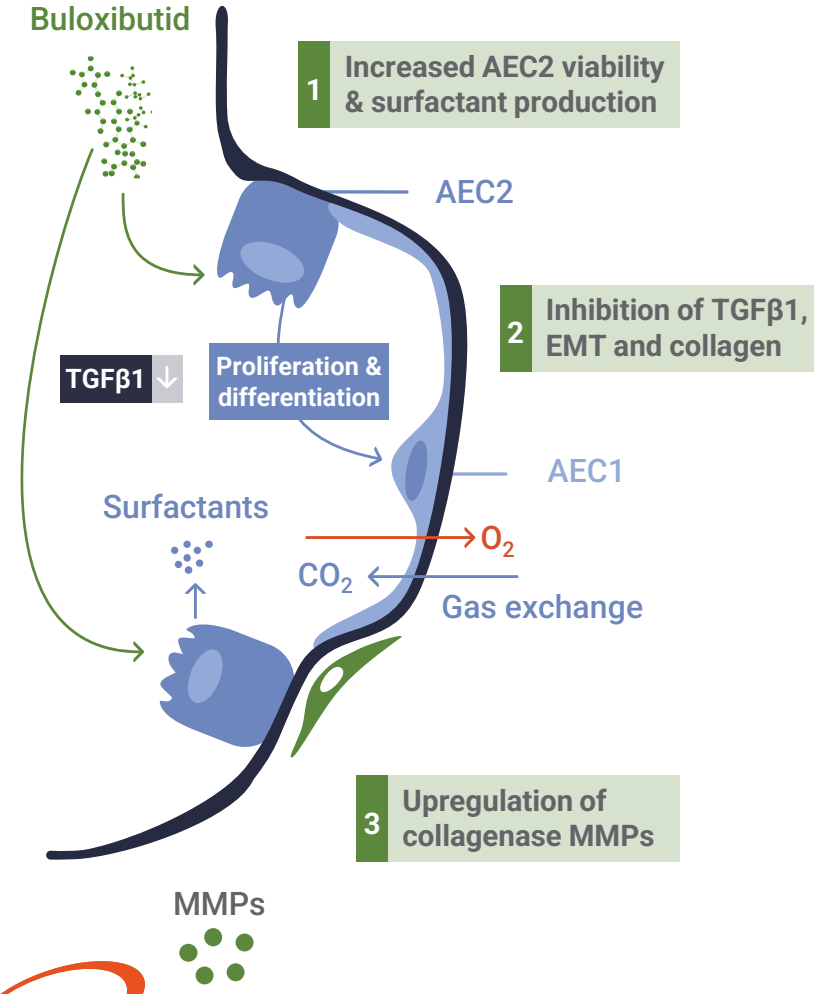
- Human precision cut IPF lung slices ± 1 µM C21
- One patient, 5 pooled lung slices

Treatment with buloxibutid protects AEC2s, increasing surfactant production to address alveolar collapse

Sources: (1) Adapted from Nalbandyan et al. FASEB 2018; (2) Vicore data on file

Buloxibutid has a potentially disease modifying MoA

Effects of buloxibutid treatment



- AT2R agonism increases AEC2 viability and surfactant production
- Restoring surfactant production can address alveolar collapse, leading to increased lung function
- Inhibition of TGFβ1 expression and signaling inhibits EMT and collagen production, halting disease progression
- Upregulation of collagenase MMPs increases fibrolysis and breakdown of collagen build-up

vicore pharma

Buloxibutid (C21) in IPF: Phase 2b ASPIRE trial design

ASPIRE

Study Characteristics

- A randomized, double-blind, placebo-controlled, parallel-group multicenter, dose-finding trial
- IPF patients on stable nintedanib/SoC or not on SoC (no access, refused, intolerant or failed)
- 52-week treatment duration; N=270 (90 per arm)
- Assessment of efficacy, safety, and pharmacokinetics at baseline as well as weeks 4, 12, 24, 36, and 52
  - Remote visits (by phone or video) to assess safety and compliance at weeks 8, 18, 30 and 44
- Primary endpoint is change from baseline in FVC at 52 weeks
- Key secondary efficacy endpoint - proportion of participants with disease progression at 52 weeks

Study Design

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

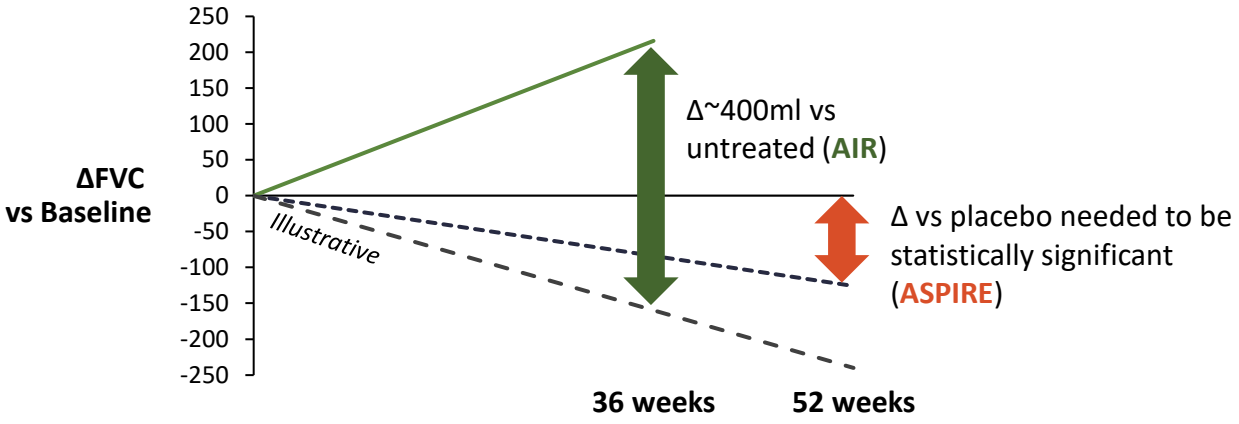
Follow-up

vicore pharma

ASPIRE is a global trial powered to demonstrate FVC stabilization

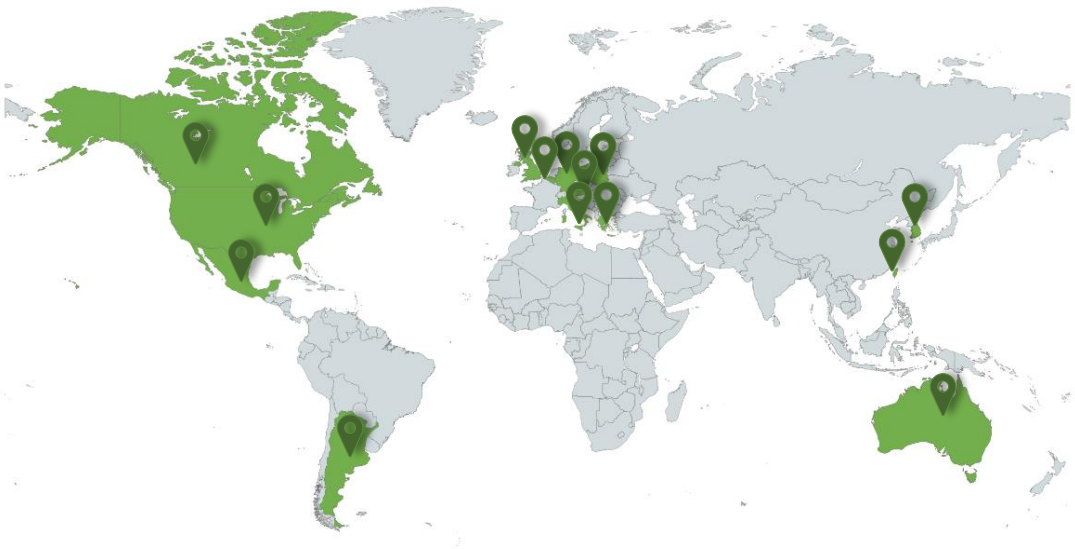
Large, conservatively powered study

- Powered to detect FVC stabilization at 52 weeks vs. conservative placebo arm assumption
- Transformative relative to standard care

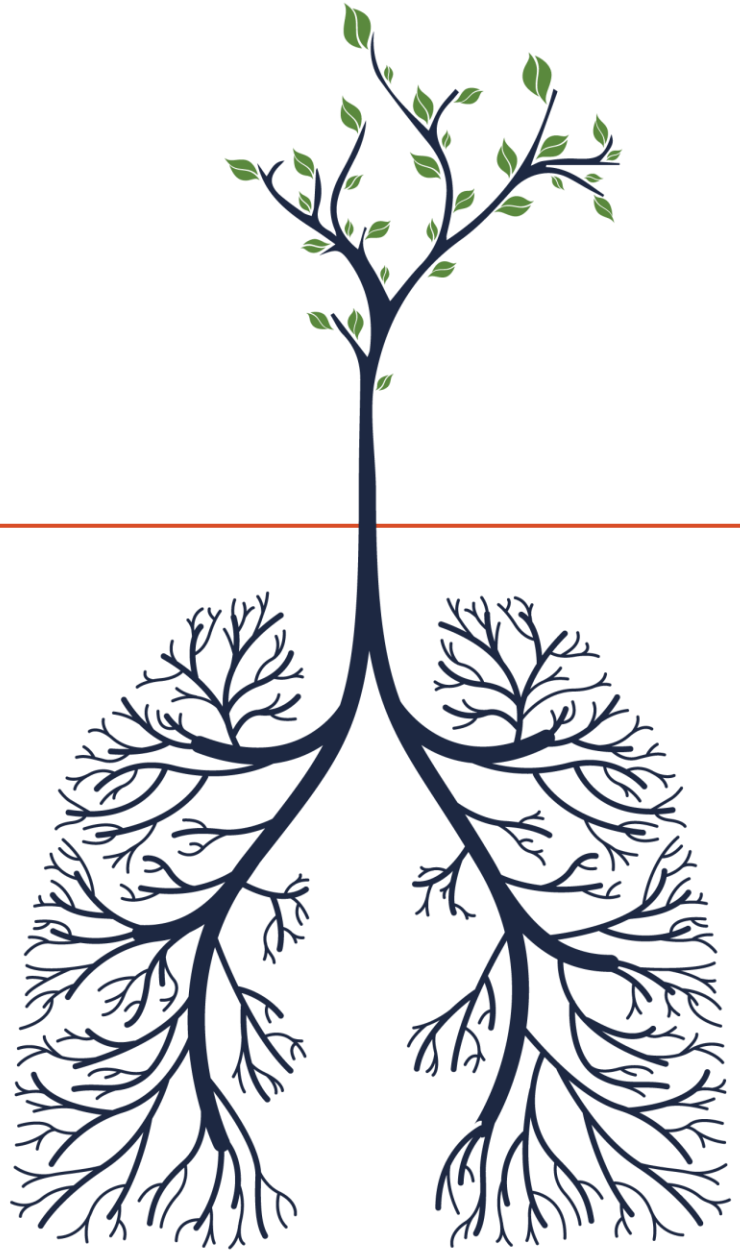


Global footprint with a broad range of countries

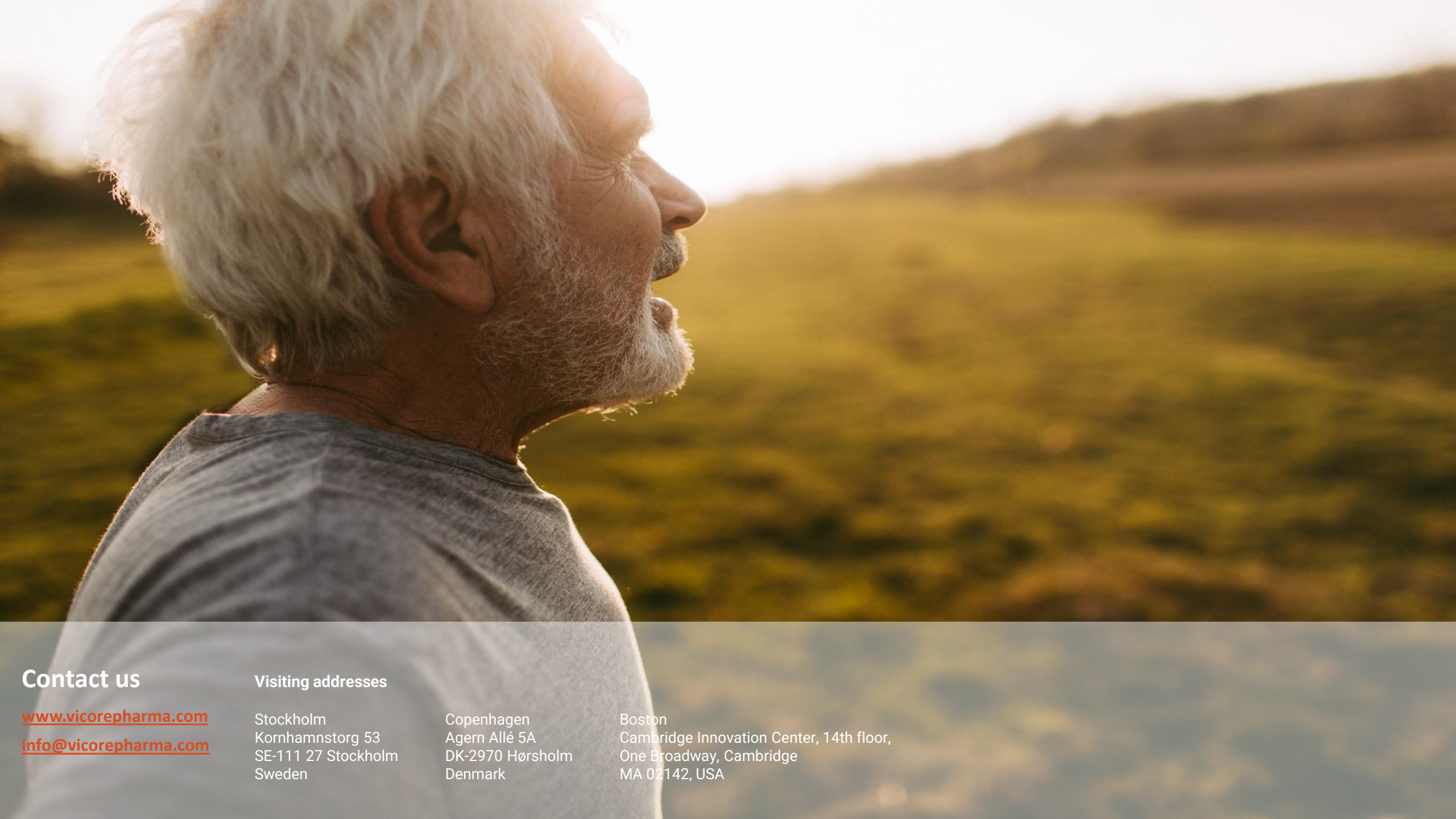
- Over 90 sites across 14 countries



Q&A Session



vicore pharma



Contact us

www.vicorepharma.com

info@vicorepharma.com

Visiting addresses

Stockholm
Kornhamnstorg 53
SE-111 27 Stockholm
Sweden

Copenhagen
Agern Allé 5A
DK-2970 Hørsholm
Denmark

Boston
Cambridge Innovation Center, 14th floor,
One Broadway, Cambridge
MA 02142, USA