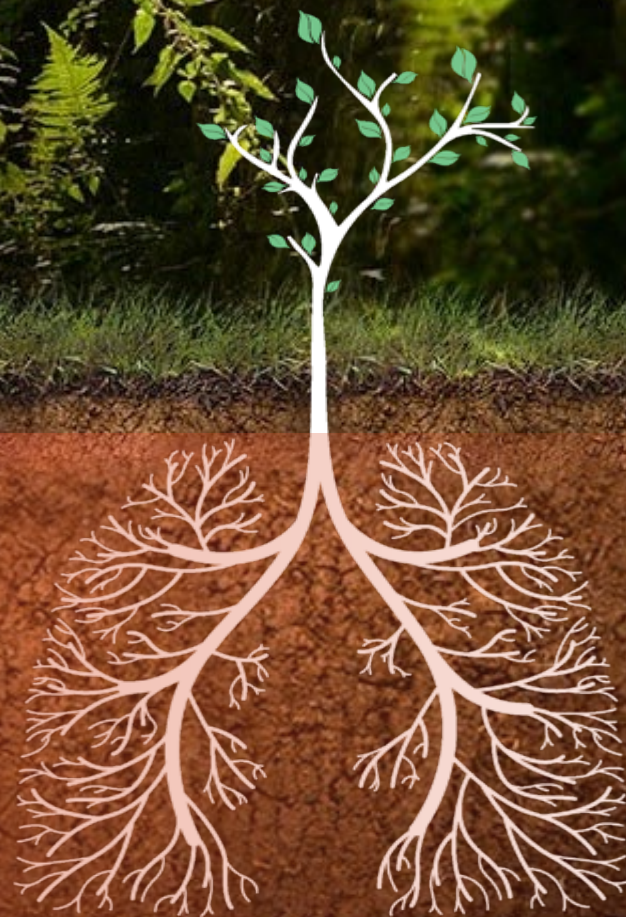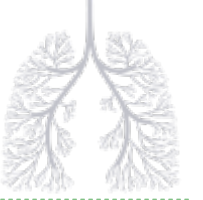**VICORE PHARMA**
AIR Interim 2 webcast

4 November 2022

Content

The AT2 Receptor

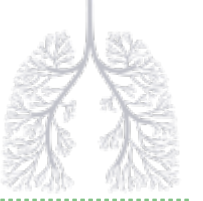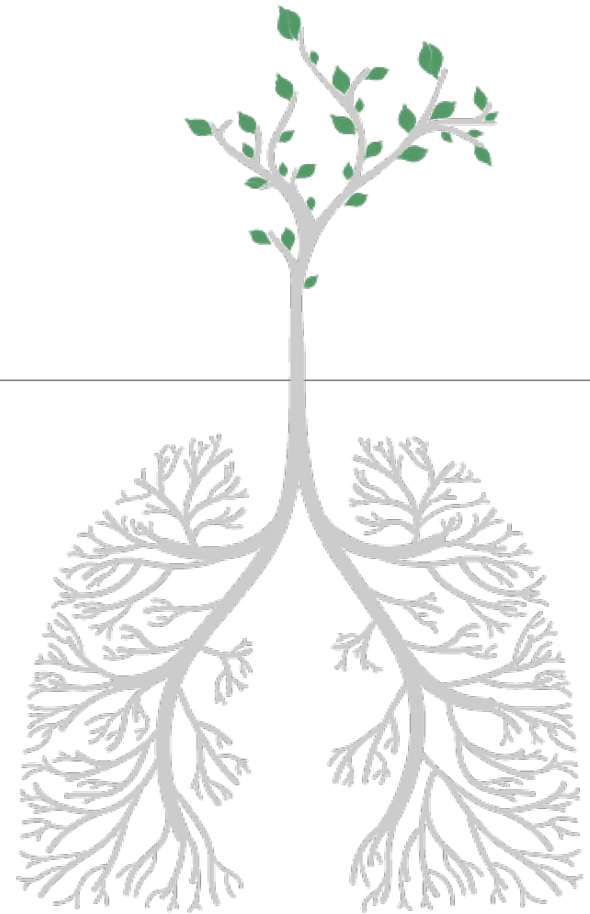C21 preclinical and clinical data

IPF and the type 2 alveolar epithelial cell (AEC2)
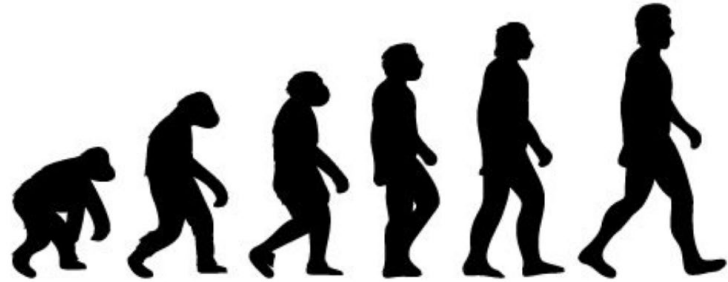
Phase 2 data IPF

The AT2 receptor

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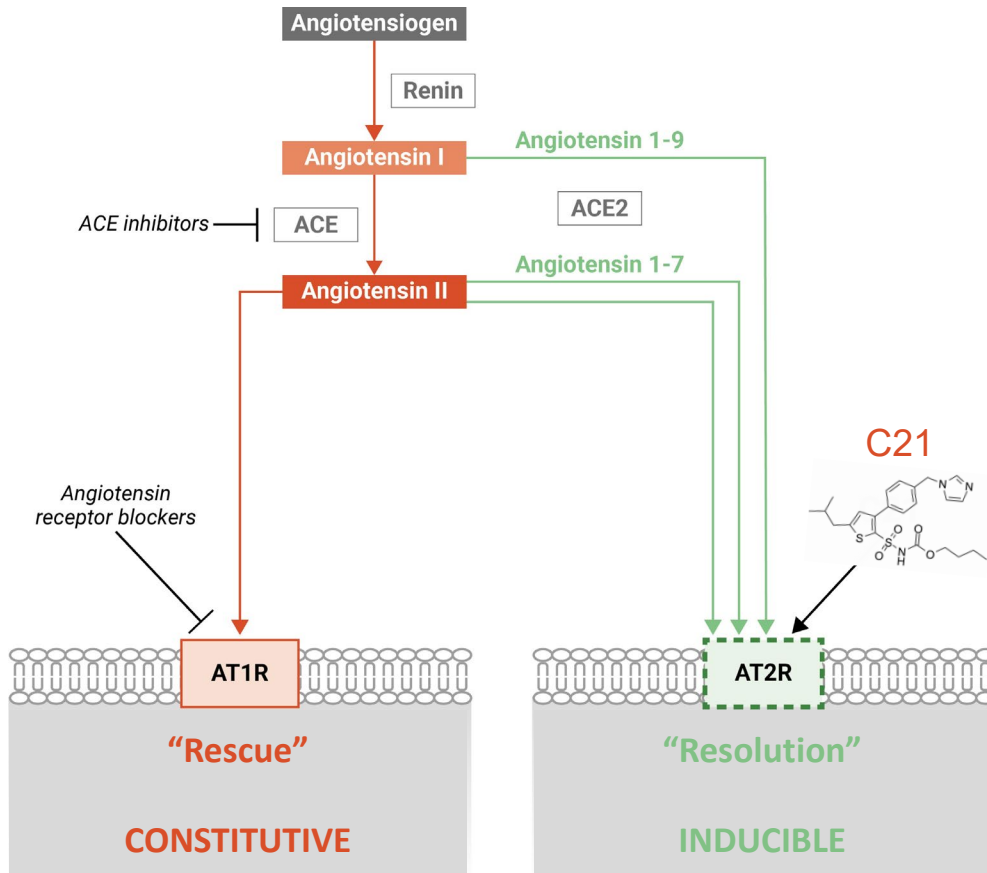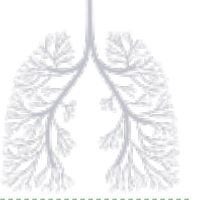# The Renin Angiotensin System (RAS) – why we have it

The Renin Angiotensin System (RAS)

- Dating back 400+ million years
- Essential for survival

Function

- Fluid and tissue homeostasis
- Prevent drop in blood pressure
- Regeneration and repair

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Angiotensin receptors as drug targets

		Function	Drug development
AT1R		Increased blood pressure	Antagonists *ACE and ARB's*
AT2R		Repair Small vessel vasodilation	Agonists *ATRAG's*

ATRAG's – Precision Pharmacology by Nature

- **Agonists** – Stimulating a repair system in the body
  - Not blocking mediator, receptor or enzyme

- **Upregulated receptor** – only present where needed
  - Not constitutive with non-selective action

- **Hit and run** – short exposure over time
  - Reduced risk for DDI and adverse events

ATRAGs – Precision Pharmacology by Nature

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C21 preclinical and clinical data

Vicore AIR interim
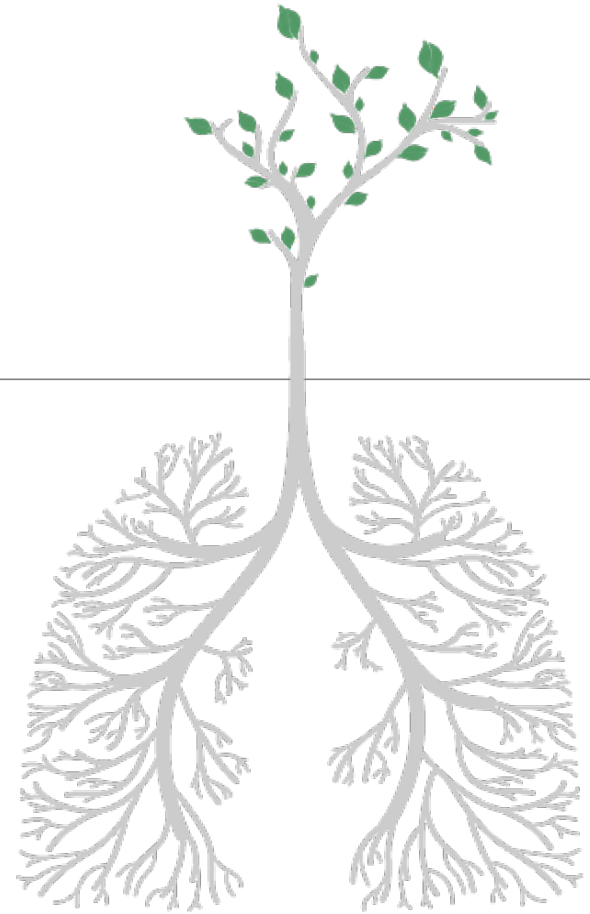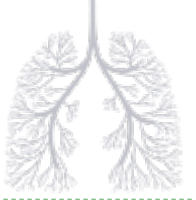
Strong preclinical evidence for C21 in IPF and PAH

Consistent results in several in-vivo animal models

C21 treatment highly effective in gold standard models:

- **Bleomycin** – IPF model

- **Monocrotaline** – IPF and PAH model

- **Sugen-Hypoxia** – PAH model

Significant and consistent effects on key parameters:

|	
↓ **Lung fibrosis**	• Collagen content (Picro-sirius staining, Hydroxyproline, Collagen gene expression)
↓ **Remodeling of pulmonary vessels**	• Ashcroft scoring • α-SMA staining • Vessel wall thickness, luminal opening and vascular lesions
↓ **Cardiac remodeling**	• Right ventricular hypertrophy (RVH)
↓ **Pulmonary hypertension**	• Right ventricular systolic pressure (RVSP) • Right ventricular end diastolic pressure (RVEDP) • Stroke volume
↑ **Cardiac output**	• mL/min

Strong data in human ex-vivo models

Human precision cut lung slices (PCLuS)

- IPF tissue collected from clinically diagnosed, biopsy confirmed IPF patients undergoing lung transplant.
- **Significant reduction of key fibrosis markers (TGFβ1 and Collagen 1)**

Human primary small airway epithelial cells

- In vitro co-culture with lung fibroblasts to mimic lung microenvironment
- **Significant reduction of key fibrosis markers (TGFβ1 and Collagen 1) and markers of fibroblast activation.**
- **Results consistent with PCLuS**

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C21 – Clinical PK and safety
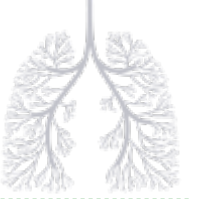
- C21 shows fast absorption, high plasma peak and fast elimination

- Linear pharmacokinetics

- Hit-and-run effect, activating the receptor to initiate a cellular response cascade

- The low exposure over time is beneficial from an induction/DDI and adverse event perspective

- Extensive cardiovascular examination including 24h Holter-ECG with no findings

- 100 mg BID has been safe and well tolerated in three phase 1 studies and in the phase 2 and 3 COVID-19 trials

C21 pharmacokinetic profile: 0.3 - 100 mg
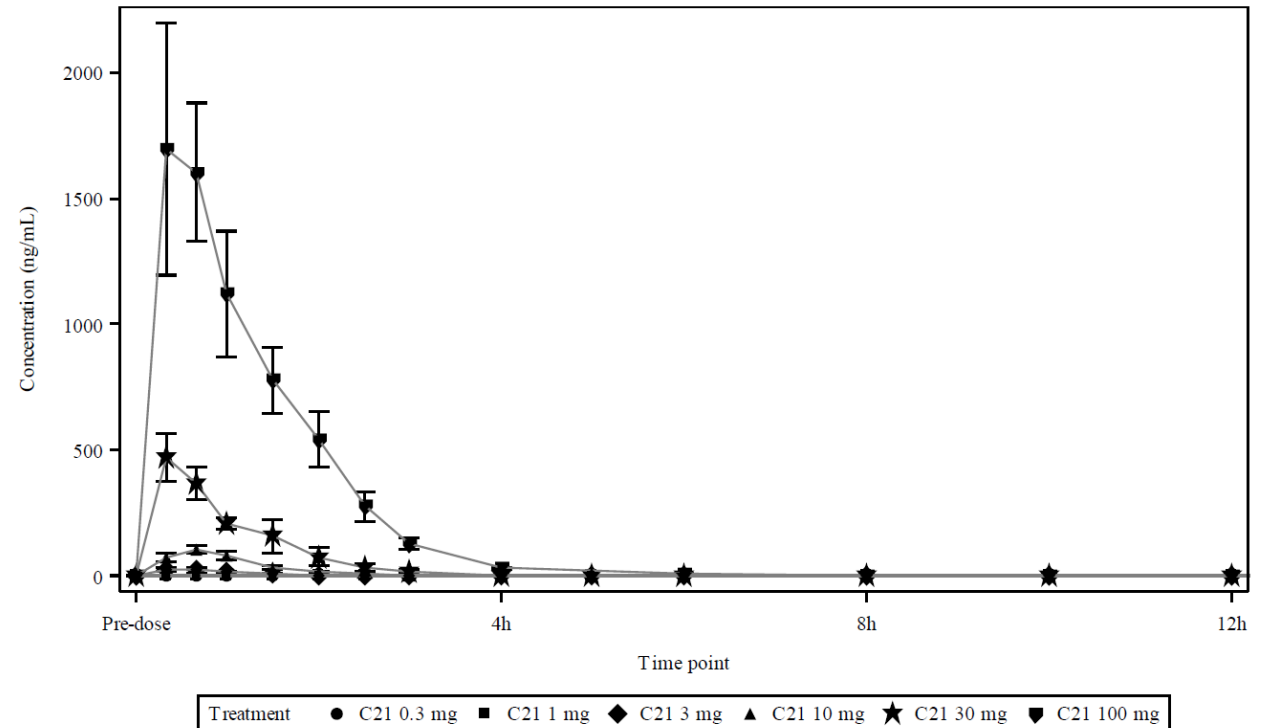
C21 PK profile shows short exposure over time
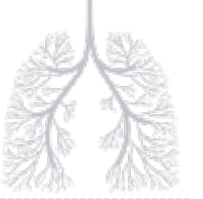
Attractive profile of C21 in IPF

Strong data in multiple preclinical models
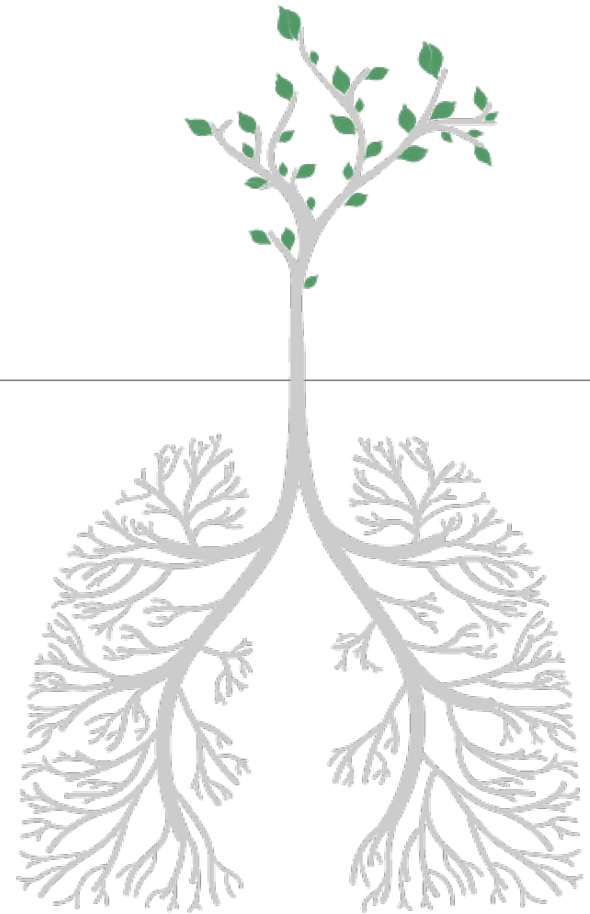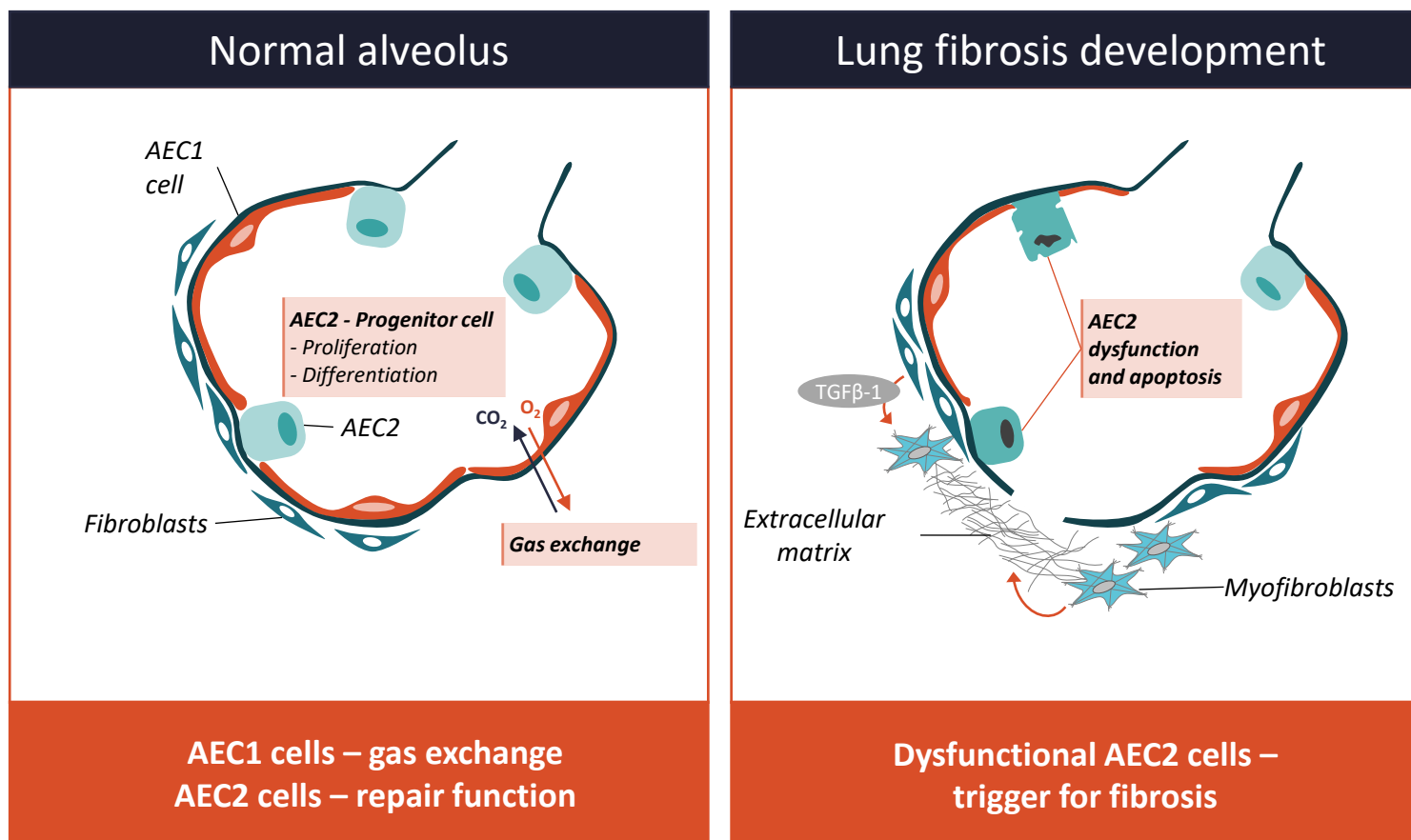
Targeting fibrosis and vasculopathy

Oral administration

Superior safety

IPF and the AEC2 cell

Vicore AIR interim

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IPF is a disease of insufficient alveolar repair leading to scarring

Normal alveolus

AEC1 cell

AEC2 - Progenitor cell
- Proliferation
- Differentiation

AEC2

CO_2 O_2

Gas exchange

Fibroblasts

AEC1 cells – gas exchange
AEC2 cells – repair function

Lung fibrosis development

TGFβ-1

AEC2 dysfunction and apoptosis

Extracellular matrix

Myofibroblasts

Dysfunctional AEC2 cells – trigger for fibrosis
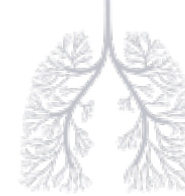
Loss of alveolar integrity is the trigger for IPF

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Human AT2R lung expression and relevance in IPF
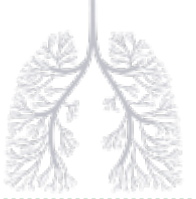
AT2R highly expressed in AEC2 cells in the lung[1]

AEC2 cells

IPF

Control

The AT2R expression in the lung supports an alveolar repair function
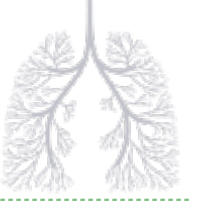
AT2R in human lung and C21 target engagement

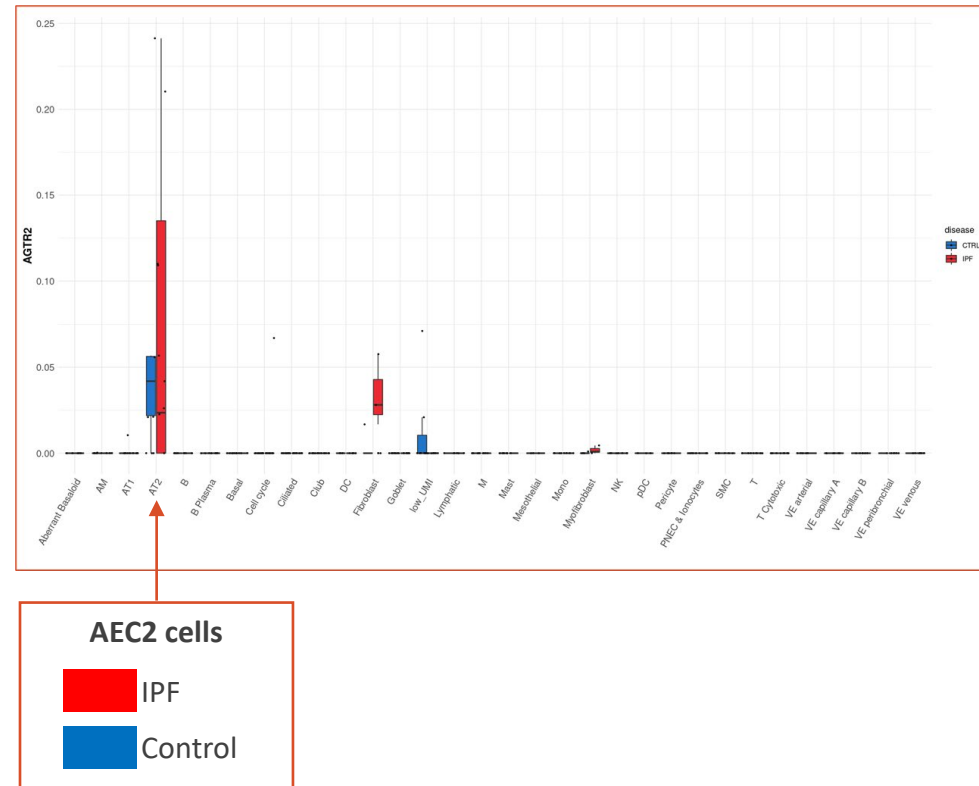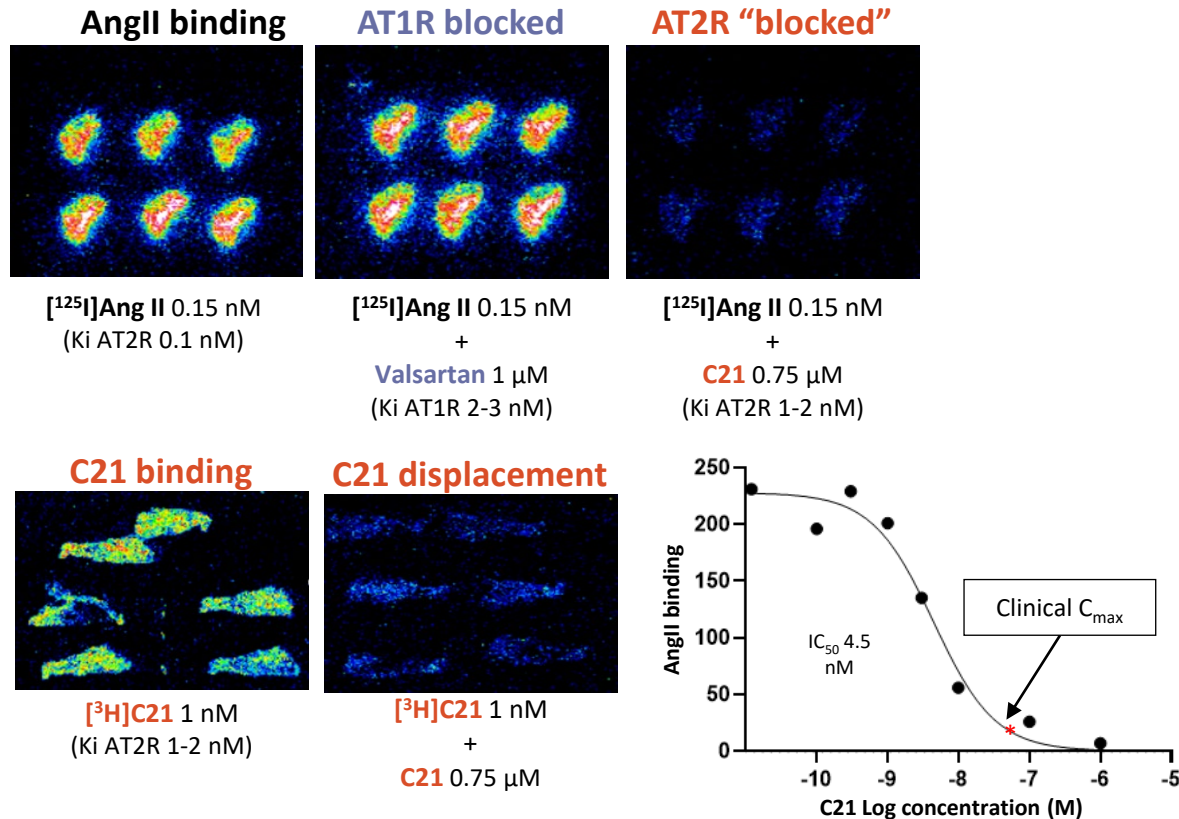## Abundant AT2R expression in human lung and specific C21 receptor binding

Receptor autoradiography performed with human lung tissue slices

AngII binding

AT1R blocked

AT2R "blocked"

[^{125}I]Ang II 0.15 nM
(Ki AT2R 0.1 nM)

[^{125}I]Ang II 0.15 nM
+
Valsartan 1 µM
(Ki AT1R 2-3 nM)

[^{125}I]Ang II 0.15 nM
+
C21 0.75 µM
(Ki AT2R 1-2 nM)

C21 binding

C21 displacement

[^{3}H]C21 1 nM
(Ki AT2R 1-2 nM)

[^{3}H]C21 1 nM
+
C21 0.75 µM

IC$_{50}$ 4.5 nM

Clinical C$_{max}$

AngII binding

C21 Log concentration (M)

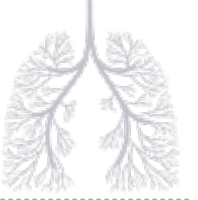## C21 inhibits TGFβ1 in human IPF lung tissue

Precision-cut human lung slices from IPF patient lung transplants

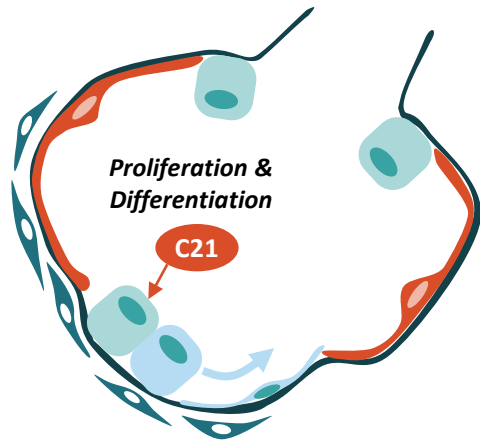TGFβ protein (% of Vehicle)

Vehicle | C21 0.01 µM | C21 0.1 µM | C21 1 µM
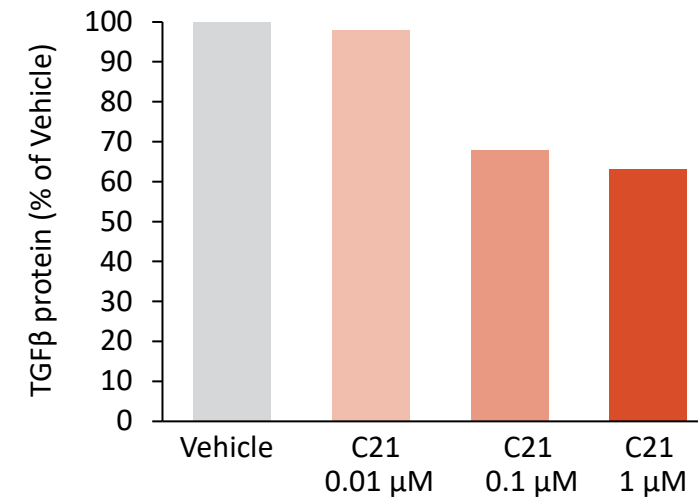
- TGFβ1 is a master regulator of fibrosis formation in IPF disease.
- Downregulation by C21 indicates strong antifibrotic properties

Source: Vicore data on file

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C21 is stimulating the AEC2 cell alveolar repair in IPF

Alveolar repair in IPF

Proliferation & Differentiation

C21

C21 stimulates AEC2 cells and alveolar repair

The AEC2 cell

- The AEC2 cell is a progenitor cell with the role to repair the alveolar integrity and prevent scarring

AT2R

- AT2R is exclusively expressed on this cell type in lung tissue and stimulation restores the alveolar integrity and lung function
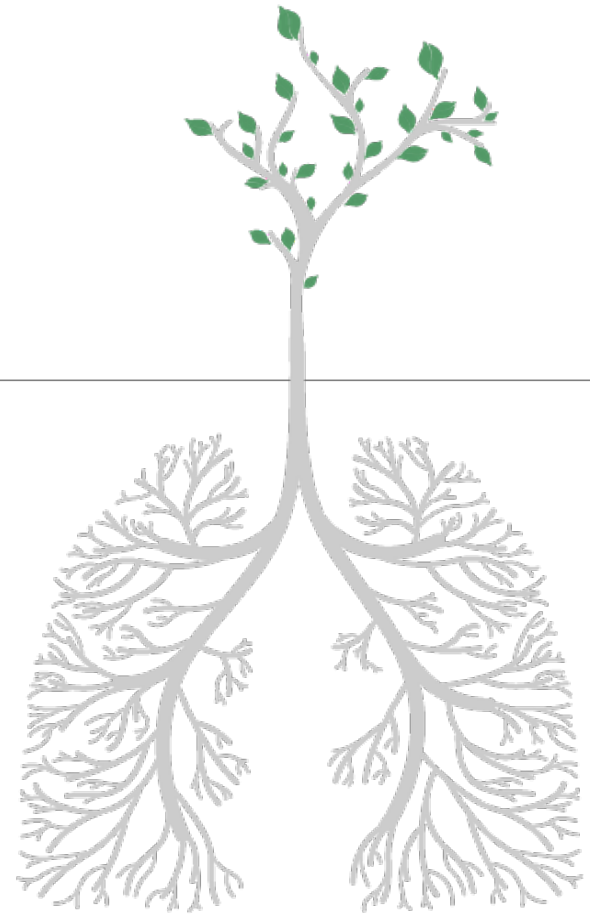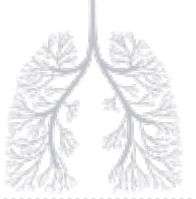
C21

- C21 is a selective AT2R agonist that stimulates alveolar repair

C21 stimulates alveolar progenitor cells to maintain alveolar integrity

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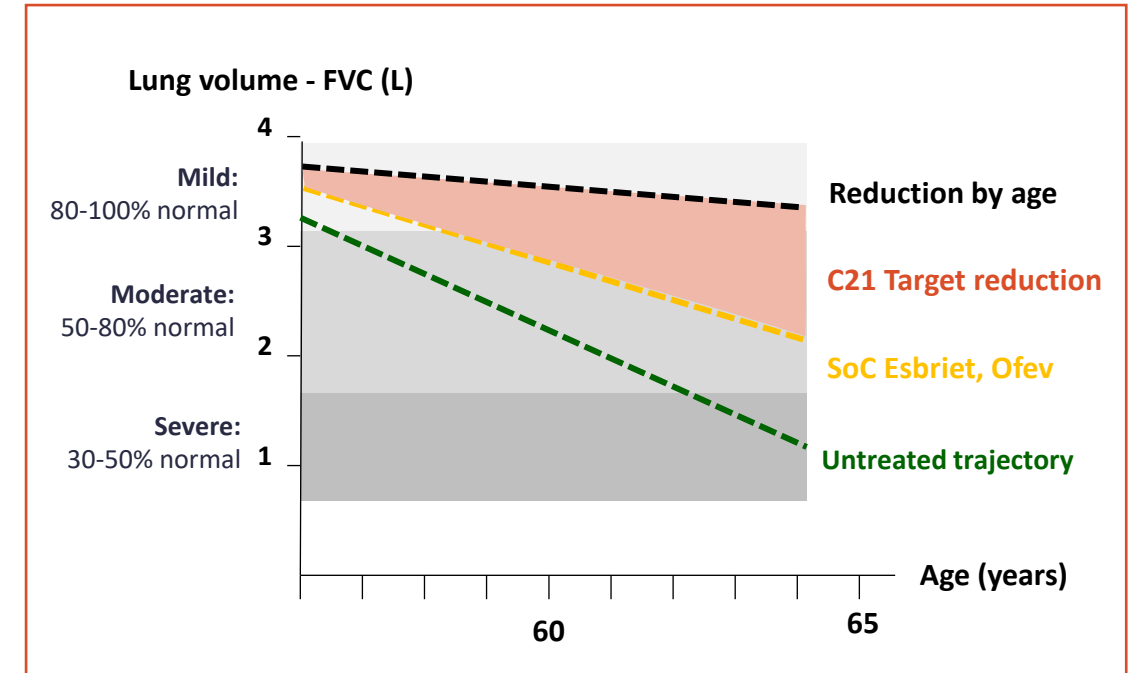# Phase 2 data IPF

Vicore AIR interim

C21 in IPF – Phase 2 AIR trial design

Study Characteristics

- Multicenter, open-label, single-arm trial
- 60 subjects with IPF
  - Central reader of HRCT to secure IPF diagnosis
  - Gold standard FVC measurement
- Primary endpoint - safety
- Primary efficacy endpoint - change in FVC at week 24 from baseline
- Treatment naïve patients, without SoC
- Untreated patients decline 120 ml/24 weeks

Lung volume - FVC (L)

Mild: 80-100% normal

Moderate: 50-80% normal

Severe: 30-50% normal

Reduction by age

C21 Target reduction

SoC Esbriet, Ofev

Untreated trajectory

Age (years)

60   65

Study Design

Screening 4 weeks	C21 100 mg oral capsule BID for 24 weeks	12 weeks treatment extension	Follow-up 4 weeks

Safety

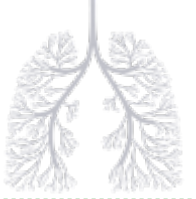| Efficacy	Efficacy

Source: Baseline data from Kolb, 2017

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AIR IPF Phase 2a data – Demography and baseline characteristics
Interim analysis October 2022

Patient characteristics

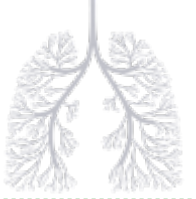|		All enrolled (N=45)
Age (years) - Mean (SD)		67.0 (9.1)
Gender	Males	33 (73.3%)
	Females	12 (26.7%)
Weight (kg) – Mean (SD)		63.4 (12.6)
BMI (kg/m^2) – Mean (SD)		24.2 (3.9)
Smoking status	Former smoker	8 (17.8%)
	Never smoker	37 (82.2%)
Duration of diagnosis (years) – Mean (SD)		0.6 (1.0)
HRCT pattern	Probable UIP	18 (40.0%)
	Typical UIP	24 (53.3%)
	Missing	3 (6.7%)

Baseline pulmonary function tests

	All enrolled (N=45)
FVC (L) - Mean (SD)	2.41 (0.69)
FVC (% predicted) - Mean (SD)	76.8 (16.0)
FEV_1/FVC - Mean (SD)	0.80 (0.07)
SpO_2 - Mean (SD)	95.5 (2.4)

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AIR IPF Phase 2a data – Patient disposition
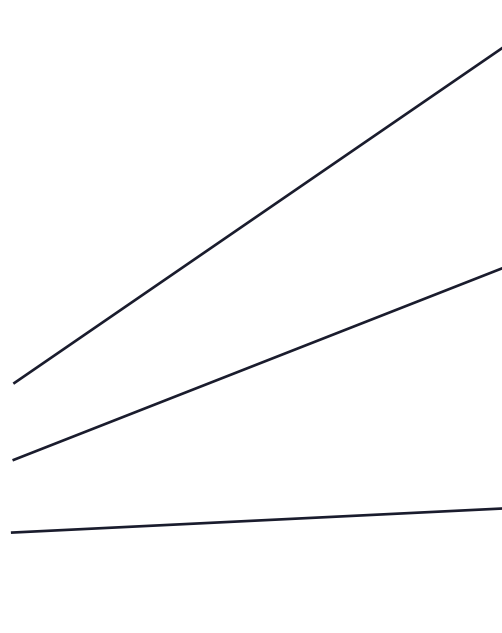Interim analysis October 2022

Enrolled (N=45)

- Ongoing: 18
- Discontinued: 18
- Completed: 9

Discontinued (N=18)

- Consent withdrawal: 9
- Adverse event: 6
- Met withdrawal criteria: 3

Consent withdrawal
- COVID-19: 2
- Logistical reasons (e.g., moving away from site): 4
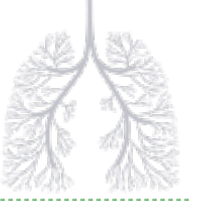- Other: 3

Adverse event withdrawal
- Abdominal pain: 1
- Death due to COVID-19: 1
- COVID-19, IPF exacerbation: 1
- Mood change: 1
- Hepatic dysfunction: 1
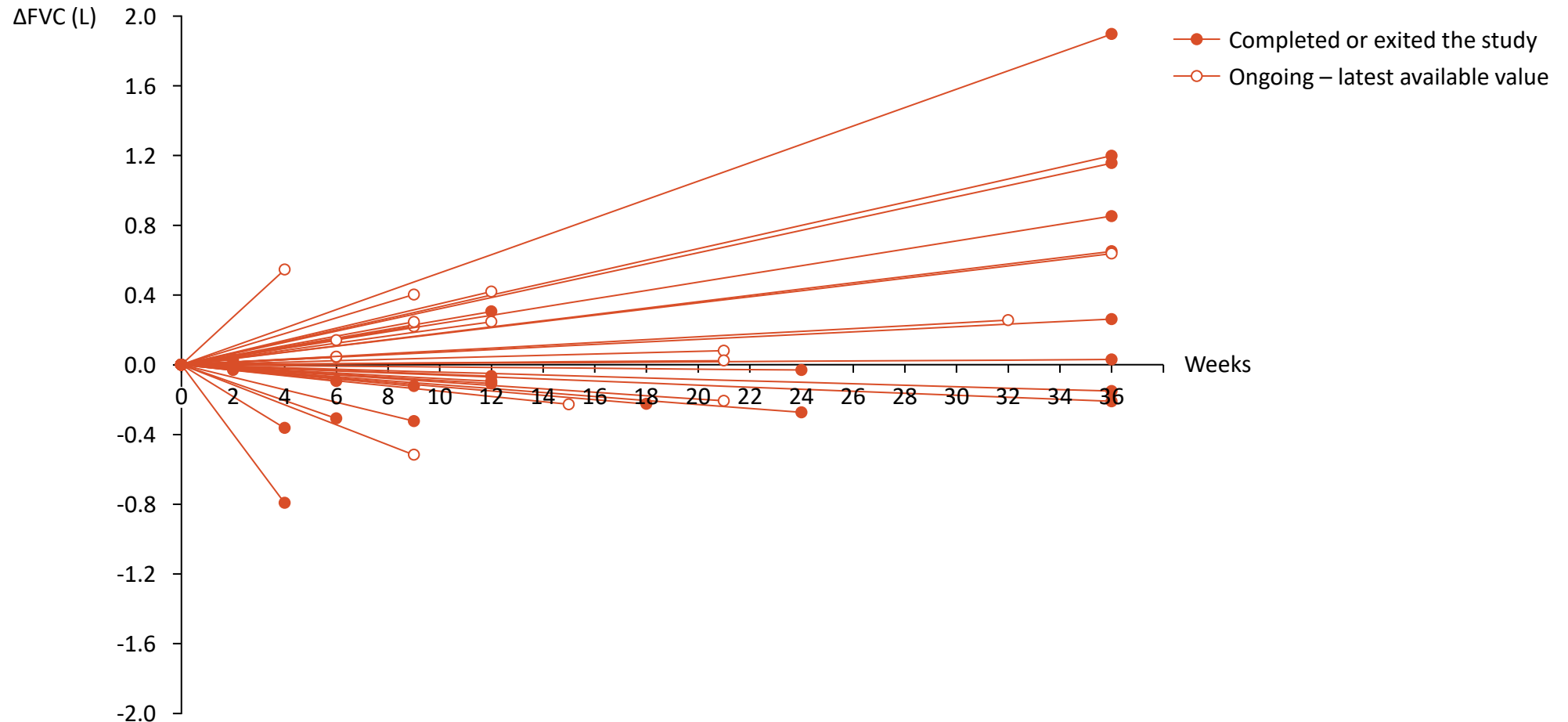- COVID-19: 1

Met withdrawal criteria
- FVC decline: 2
- Subject not able to perform spirometry due to cough: 1

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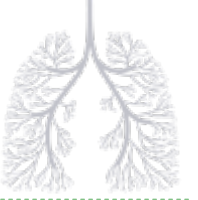# Individual patient values at time of analysis

Interim analysis October 2022

Change in FVC from baseline (L) – individual patient values at time of analysis (completed and ongoing subjects)
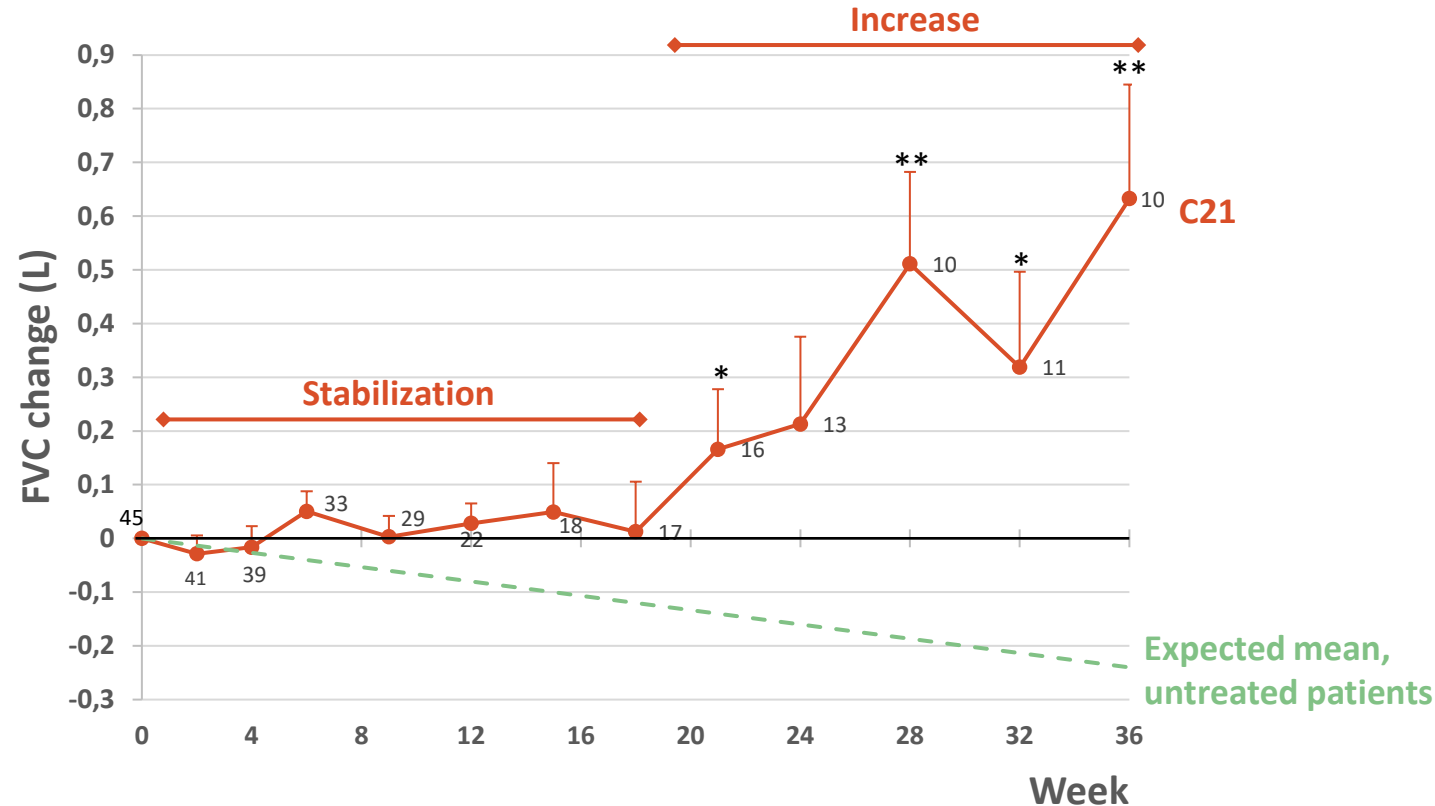
Mean change (±SEM) from baseline in FVC over time, observed values

- Safe and well tolerated – no GI signals
- 213 mL increase in FVC at 24 weeks
- Stabilizes disease at 6 weeks
- Increases lung function as of 18 weeks
- Encouraging patient testimonies

Slope values at 21, 28, 32 and 36 weeks are statistically significant ($*p<0.05$ and $**p<0.01$) vs. the expected mean for untreated patients.
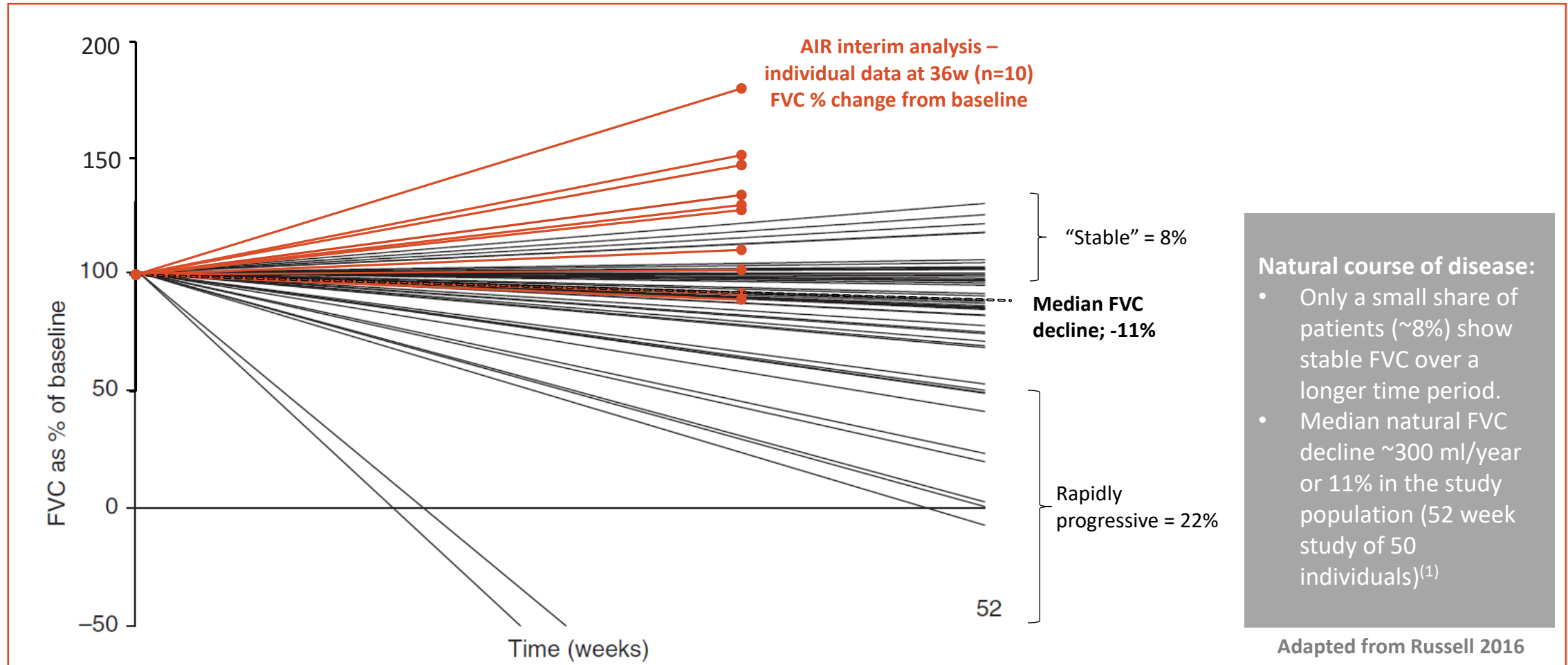
The AIR interim results show early stabilization of FVC with later increase in lung function

Note: SoC estimated based on Nintedanib INPULSIS trials (Source: N Engl J Med 2014; 370:2071-2082). Expected mean untreated patients based on placebo data from previous clinical trials.
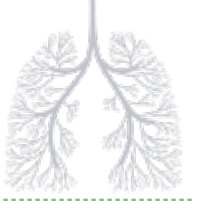
20

Natural FVC decline in patients with IPF (Linear regression based on observed values) – overlay with AIR data Interim analysis Oct 2022


AIR interim analysis – individual data at 36w (n=10) FVC % change from baseline

"Stable" = 8%

Median FVC decline; -11%

Rapidly progressive = 22%

FVC as % of baseline

Time (weeks)

Natural course of disease:
- Only a small share of patients (~8%) show stable FVC over a longer time period.
- Median natural FVC decline ~300 ml/year or 11% in the study population (52 week study of 50 individuals)[1]

Adapted from Russell 2016

The increase in FVC seen in AIR is markedly different from the natural decline

Source: (1) Russell et al Am J Resp Crit Care Med, 194, 8, 2016
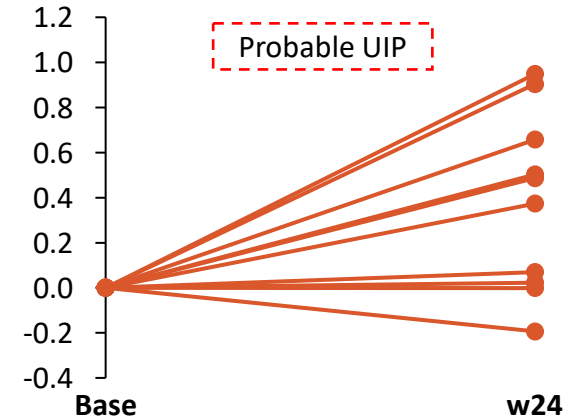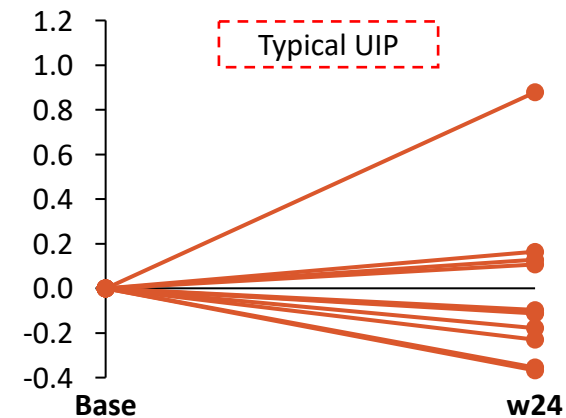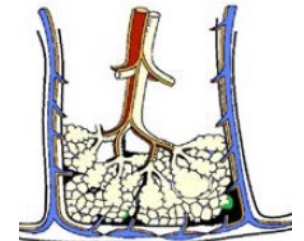
**Individual rates of decline in FVC scaled to 24 weeks, linear regression in patients with 12-week data (n=22)**
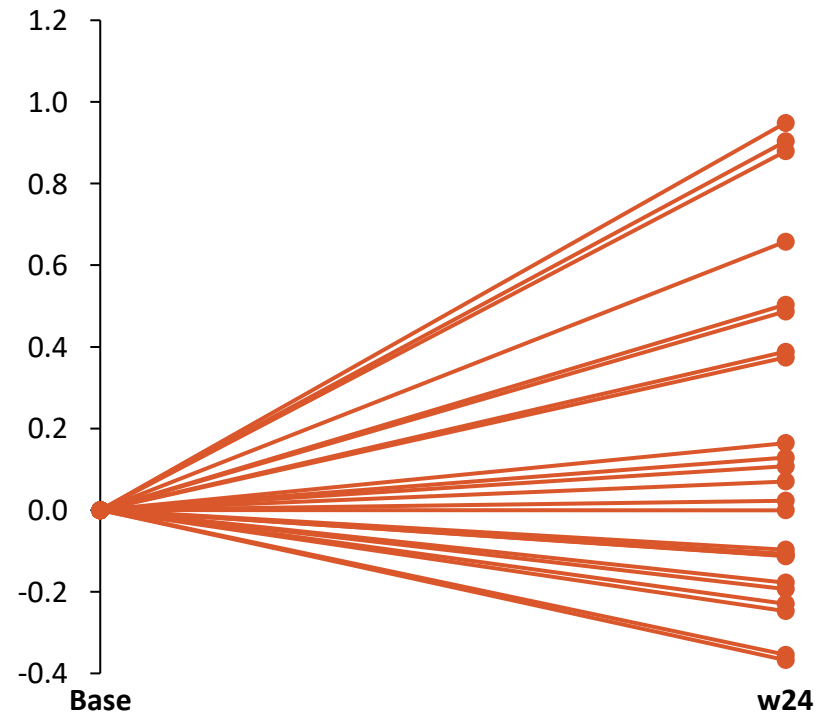
Individual rates of decline in FVC scaled to 24 weeks, linear regression in subjects with 12-week data, by HRCT pattern
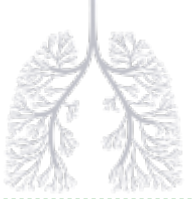
Probable UIP

Typical UIP

Probable UIP: patchy fibrosis, only mild architectural destruction

**Typical UIP:** wider fibrosis, thickened walls, and honeycomb cysts
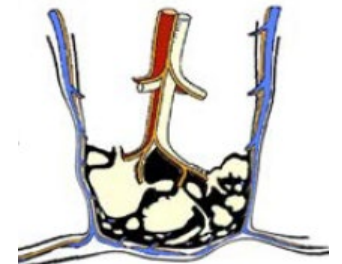
The increase in FVC is more pronounced in patients with probable UIP

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Summary of adverse events in AIR interim analysis vs INPULSIS 1

|	INPULSIS 1; 52-week treatment		AIR interim analysis Oct-22	
	Nintedanib	**Placebo**	**C21**	
	n=309	**n=204**	**n=45**	
	%	**%**	**%**	
Any AE	96	89	58	
Common AEs (Non-exhaustive)				
Diarrhea	62	19	2	
Nausea	23	6	4	
Progression of IPF	10	10	2	
Cough	15	13	4	
Vomiting	13	2	2	
COVID-19	n/a	n/a	7	n=3
Alopecia	n/a	n/a	16	n=7
Fatal AE	4	5	2	n=1 (COVID)
Severe AE	26	18	4	n=2 (COVID, IPF exacerbation)
Serious AE	31	27	7	n=3 (COVID, IPF exacerbation, sqamous cell carcinoma of the mouth)
AE leading to discontinuation	21	11	20	
Related AE			18	

C21 caused no serious adverse events and lacks GI side effect profile

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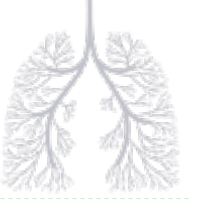
Drop-outs – AIR per October 2022

Subject	Week	Patient withdrawal	Protocol	Comment
1	8	Y	Withdrew consent	Afraid of COVID-19
2	12		SAE, not related	Died of COVID-19
3	6		Met withdrawal criteria	Cough
4	2	Y	Withdrew consent	
5	2	Y	AE, related	Mild abdominal pain
6	24	Y	Withdrew consent	Afraid of COVID
7	10	Y	Withdrew consent	Relocated
8	21	Y	AE, not related	Liver dysfunction
9	4	Y	Withdrew consent	
10	12		AE not related	COVID-19, exacerbation
11	24	Y	AE not related	COVID-19
12	3	Y	Withdrew consent	
13	10	Y	AE not related	Low mood
14	6		Met withdrawal criteria	Bronchitis
15	8	Y	Withdrew consent	Relocated
16	12		Met withdrawal criteria	
17	8	Y	Withdrew consent	Relocated
18	4	Y	Withdrew consent	

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Individual patient stories
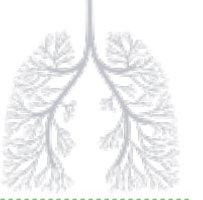
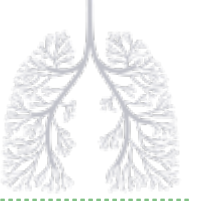Patient is extremely happy urged to continue on drug

Patient's quality of life improved – requested PI to let him continue on drug after the study

Had extreme dry cough that after treatment subsided

Dry cough subsided after treatment

Patient improved in general health condition

Patient very happy with treatment, can breathe sleeping on stomach

C21 in IPF – IPF Phase 2 Interim data (October 2022) in summary

Stabilizes disease from week 6

Increases lung function from week 18

Safe and well tolerated – no GI side effects

Encouraging patient testimonies

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Vicore is well positioned to develop a new class of drugs for rare lung diseases and beyond