

Interim Analysis of AIR - An Open-label, Single Arm, 36-week Phase 2a Trial of the Angiotensin II Type 2 Receptor Agonist (ATRAG), C21, in Individuals with IPF



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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and fatal interstitial lung disease. The incidence is estimated to be 2.8 to 19 per 100,000 people per year and increasing with age.¹ Debilitating symptoms of IPF typically appear between ages 50 and 70 years most commonly in men, but the incidence is increasing in women.¹ A yearly decline in lung function, as measured with in forced vital capacity (FVC) of 240 mL is expected in untreated individuals with IPF based on a large placebo-controlled trial.²

To date, no therapy has been shown to halt the progressively declining lung function associated with IPF and available therapies are poorly tolerated. Current therapies for IPF have limited efficacy, with severe side effects leading to treatment discontinuation in up to 50% of patients.³ Despite the availability of current treatments for IPF, an unmet medical need remains for effective and well tolerated new treatments.

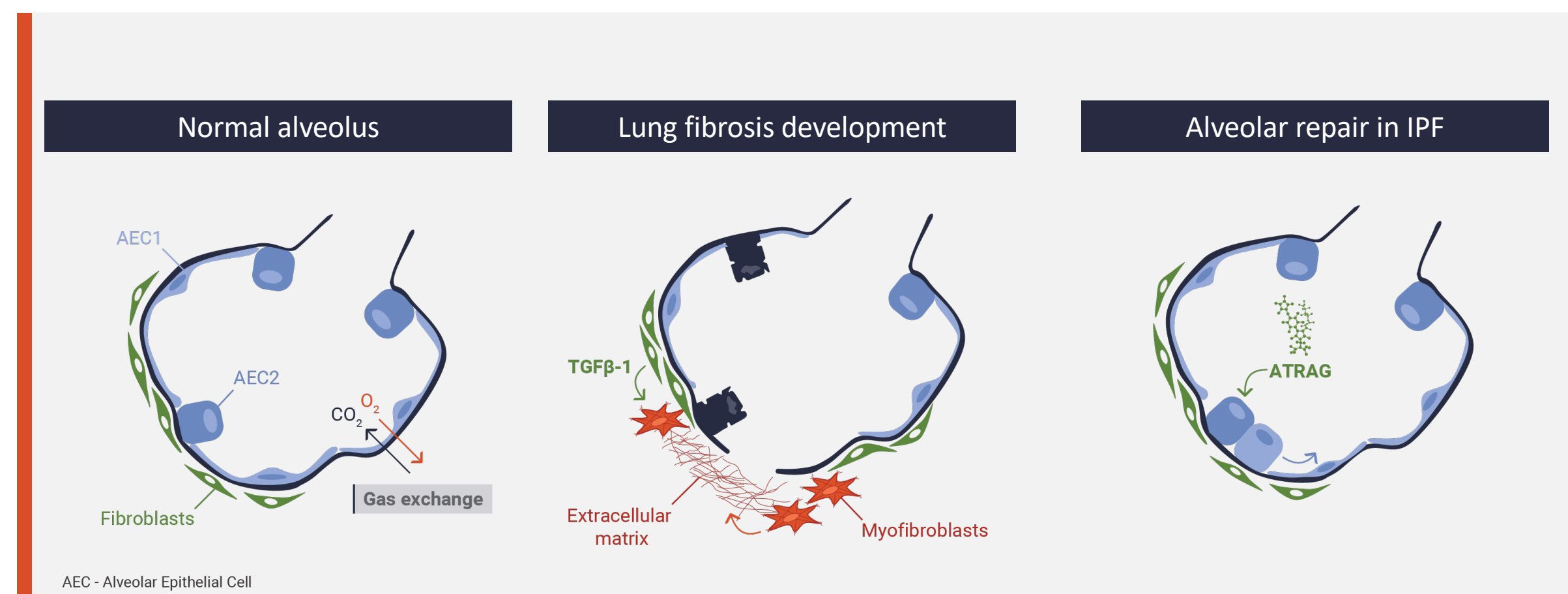


Figure 1. Mode of action of angiotensin II type 2 receptor agonists (ATRAGs) in IPF: promoting alveolar repair and integrity through alveolar epithelial type 2 (AEC2) cells

- In IPF, alveolar epithelial type 2 cells (AEC2) become dysfunctional and lose their ability to repair and maintain alveolar integrity. This loss of integrity triggers release of profibrotic mediators, which initiate fibrosis development.^{4,5} (Figure 1)
- Angiotensin II type 2 (AT2) receptors are highly expressed in the alveolar epithelial cells in the adult human lung and can be upregulated during repair and regeneration.⁵
- C21 is a first-in-class, low molecular weight, orally bioavailable, specific, high-affinity angiotensin II type 2 receptor agonist (ATRAG).^{7,8}
- By activating AT2 receptors, C21 stimulates protective signaling pathways, promoting alveolar repair and maintenance of alveolar integrity, with resulting beneficial effects reducing fibrosis formation, inflammation, and pulmonary hypertension.⁶⁻¹³
- In Phase 1 trials, C21 administered orally at 100 mg twice daily has been shown to be well tolerated with a favourable safety profile and the pharmacokinetic (PK) profile supports twice daily dosing.

Methods

- AIR is an ongoing Phase 2, multi-centre, open-label, single-arm, 36-week international trial (Figure 2).
- The objectives are to evaluate the safety, efficacy, and PK of C21 in patients with IPF at an oral dose of 100 mg twice daily.
- Treatment-naïve individuals or individuals who have stopped anti-fibrotics after up to 6 months treatment not due to disease progression, are enrolled.
- Individuals diagnosed with IPF in accordance with either ATS/ERS/JRS/ALAT/Fleischner criteria within the last 5 years and a percent predicted FVC of 60% or higher are eligible.
- Confirmation of IPF diagnosis on HRCT (High-Resolution Computed Tomography) scan (typical/probable UIP) centrally confirmed by an independent expert radiologist at national center for thoracic disease in UK.
- Spirometry is centralised with best test review (Clario, Philadelphia, PA, USA).
- For each participant, a treatment evaluation assessing the benefit-risk to continue in the trial is conducted by the investigator at 12 and 24 weeks.
- Efficacy endpoints include change from baseline in FVC over 24 and 36 weeks.
- Change in FVC scaled to 24 weeks was summarised as 3-visit rolling averages, with and without imputation of missing data. Imputation of withdrawals was done assuming an untreated FVC decline of -120 mL/24 weeks. No imputation for ongoing participants.
- Automated quantification of lung, airway, vessel, and fibrosis volumes on screening HRCT scans was conducted.
- Safety data were evaluated at regular intervals by an independent data monitoring committee.

References
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AIR trial design

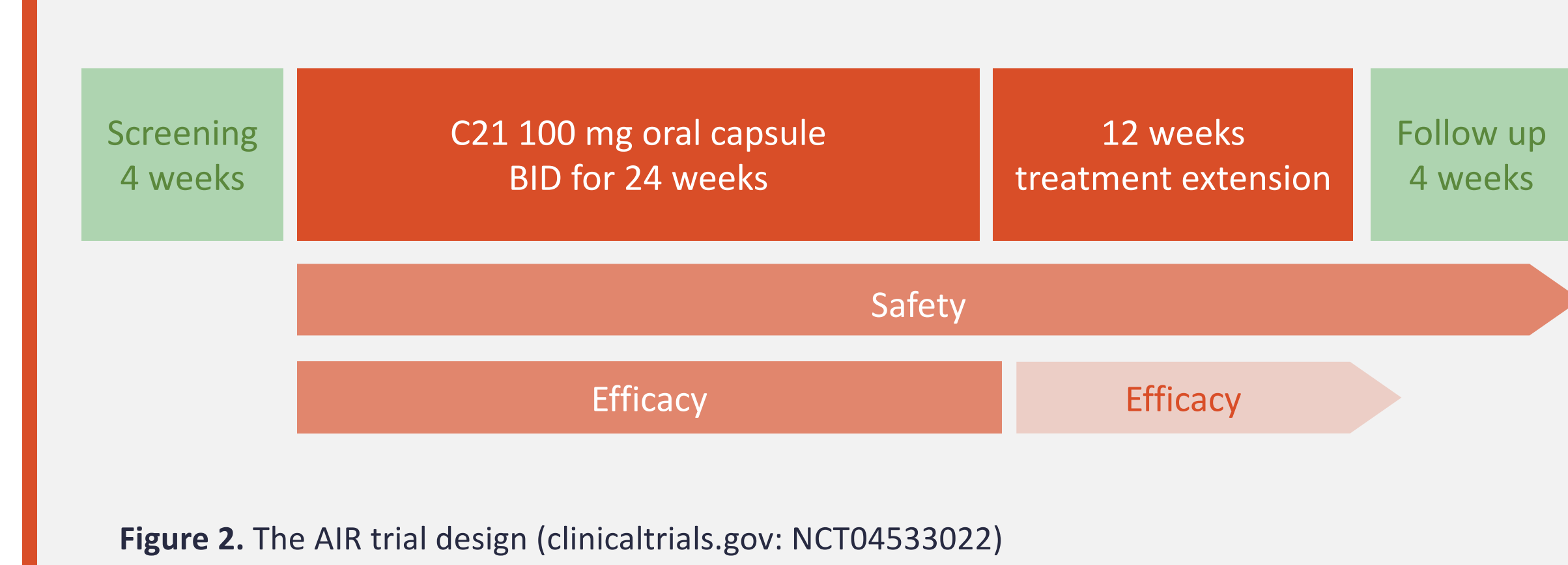


Figure 2. The AIR trial design (clinicaltrials.gov: NCT04533022)

Results

This was an interim analysis on the first 51 participants in the trial – all were treatment-naïve with respect to anti-fibrotics (Table 1). Efficacy was assessed in the 46 patients who had at least 2-weeks FVC data.

- Treatment with C21 resulted in stabilization of FVC at 24 weeks and an increase at 36 weeks (Figure 3), with 8 high responders (defined as an annual rate of FVCpp increase ≥ 10) at each of the two timepoints.
- Quantitative HRCT analysis showed that high FVC responders at 24 weeks had lower airway volumes than remaining individuals ($p=0.02$) (Figure 5).

		All treated (N=51)
Age (years) - Mean (SD)		67.6 (9.1)
Gender	Males	76.5%
	Females	23.5%
Ethnicity	White	27.5%
	Asian	72.5%
BMI (kg/m ²) - Mean (SD)		24.5 (4.1)
FVC % predicted - Mean (SD)		75.3 (13.8)
Previous use of anti-fibrotics	Pirfenidone	0%
	Nintedanib	0%

Table 1. Demographic and baseline characteristics

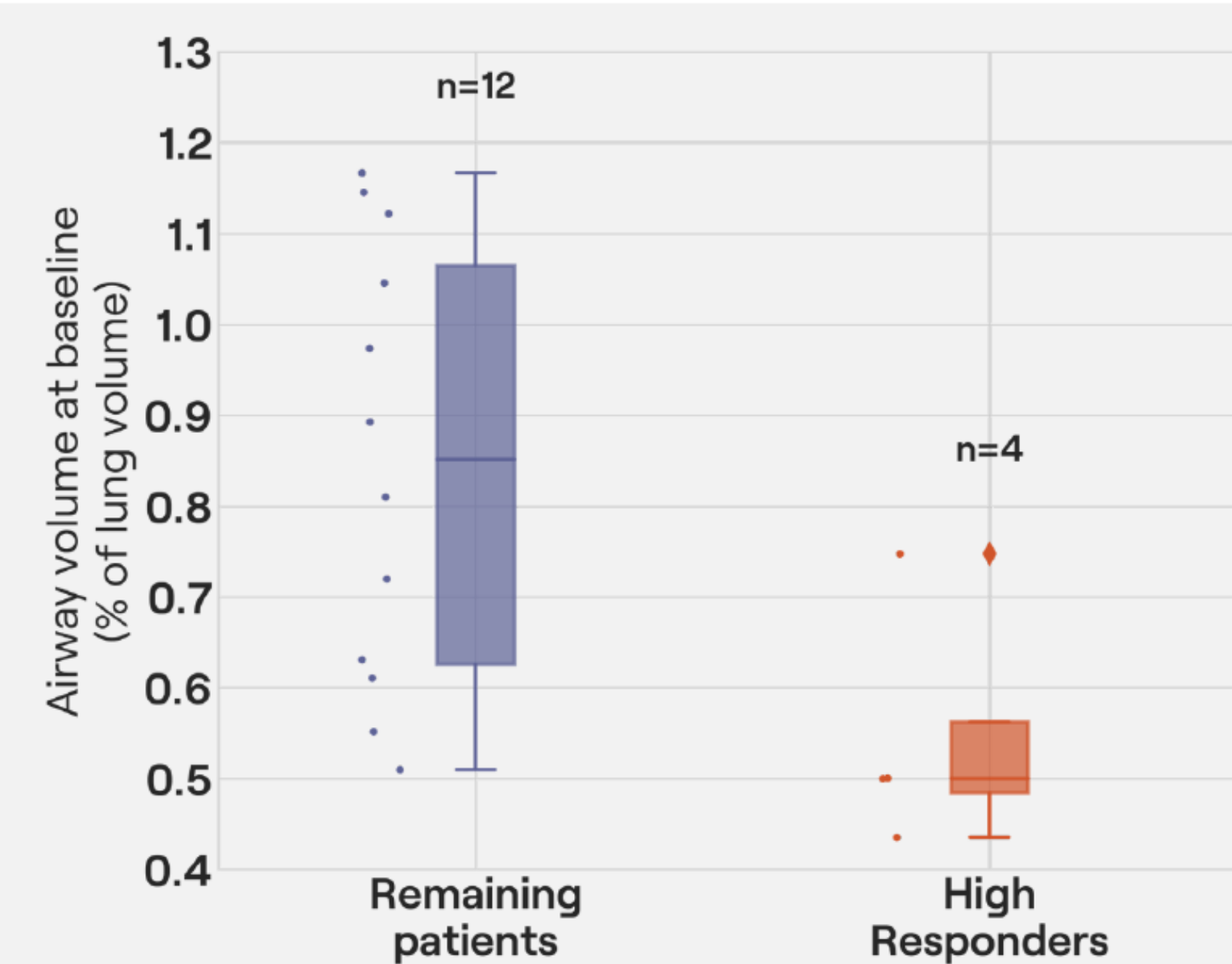


Figure 5. Normalized airway volume for patients at 24-week endpoint, showing difference between patients with improving FVC (high responders) and the rest of the cohort. Difference is significant – Mann Whitney p-value 0.02

Abbreviations
 AEC2: Alveolar Epithelial type 2 Cells
 ATRAG: Angiotensin II Type 2 Receptor Agonist
 FVC: Forced Vital Capacity
 HRCT: High-Resolution Computed Tomography
 IPF: Idiopathic Pulmonary Fibrosis

Consistent FVC stabilization

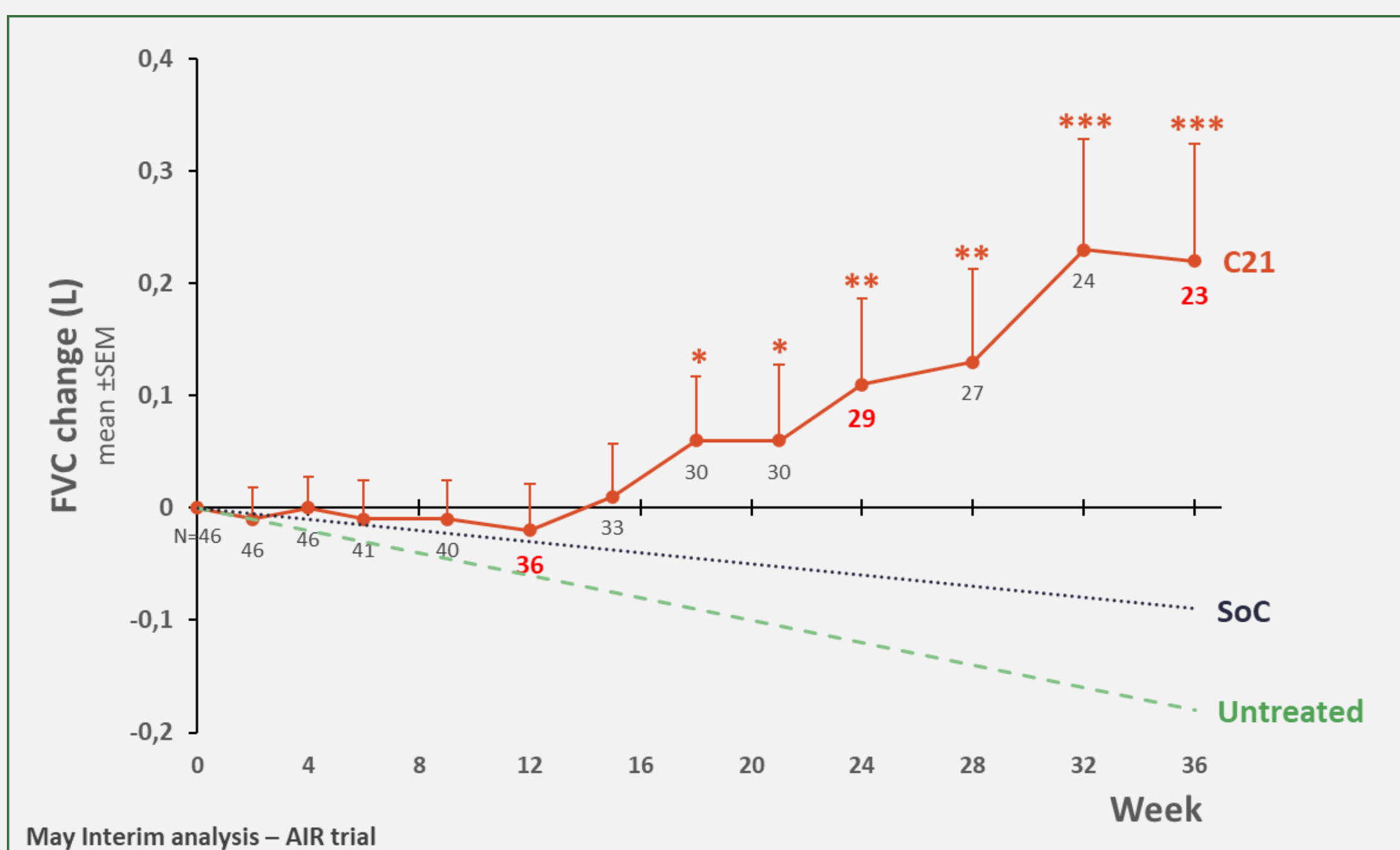


Figure 3. n=46 patients with 2-week data. 3-visit rolling average, no imputation. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ FVC scaled to 24 weeks vs change of -120 ml (untreated)

FVC stabilization over time, even with conservative imputation

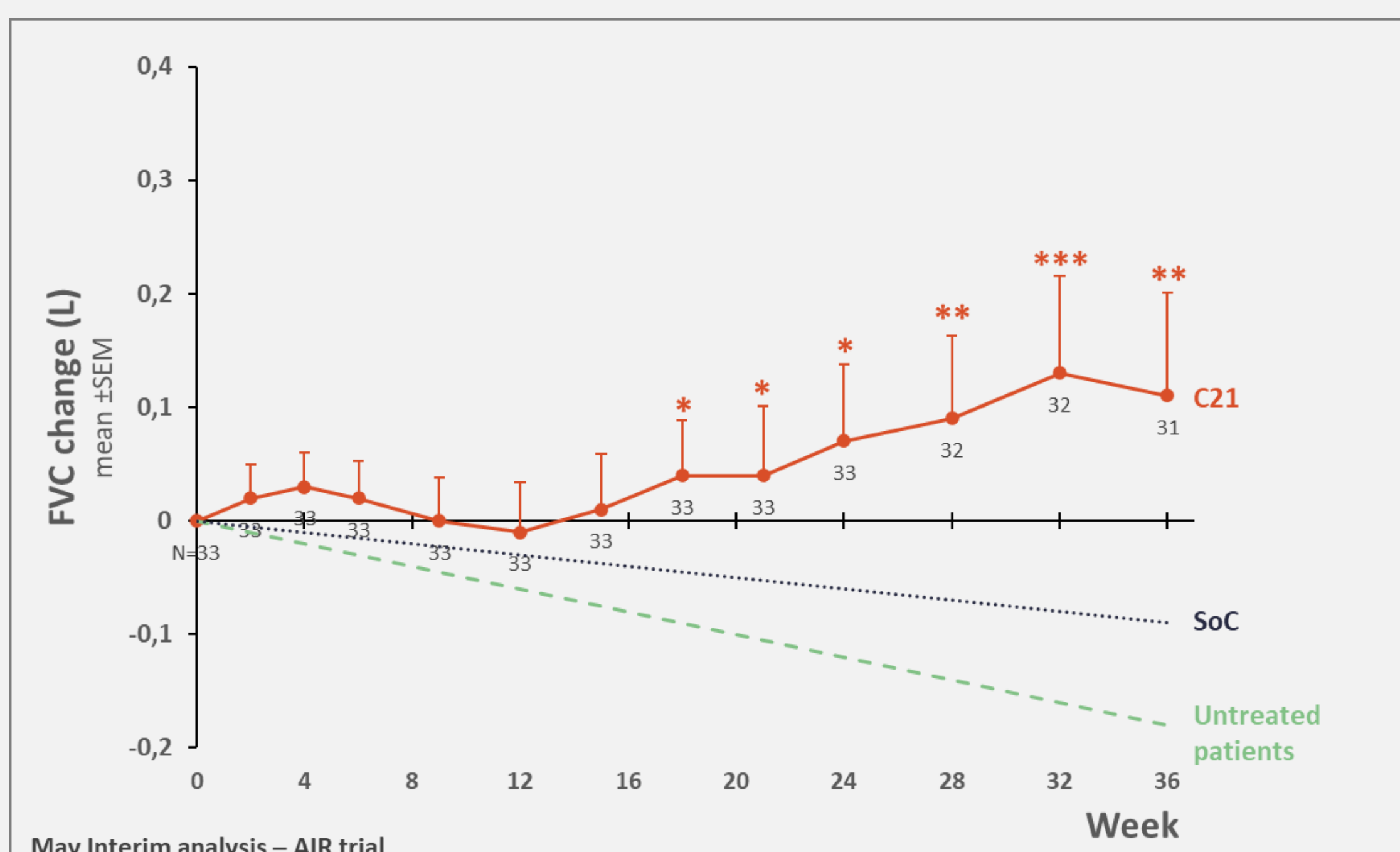


Figure 4. n=33 patients with 12-week data. 3-visit rolling average. All patients with 12-week data that discontinued the study were assigned a decline in FVC of -120ml/24 weeks (i.e. normal disease progression). No imputation for ongoing patients. * $p<0.05$, ** $p<0.01$ *** $p<0.001$ FVC scaled to 24 weeks vs change of -120 ml (untreated)

Safety and tolerability

C21 was well tolerated without treatment-related serious adverse events or gastrointestinal toxicity.

- The most common adverse event was mild to moderate hair loss (8 patients)
- 7 participants continued C21 despite hair loss events, which resolved during continued C21 treatment in 4 participants
- 5 patients reported serious adverse events which were all considered unrelated to C21.

Summary and Conclusions C21 in IPF – promising interim data

- C21 stabilized FVC at 24 weeks and improved lung function in the longer term, particularly in individuals with early disease as indicated by lower airway volumes, suggesting less traction bronchiectasis.
- The results are in line with a reparatory mechanism of action of C21 – the first-in-line ATRAG.
- C21 has a favorable safety and tolerability profile without gastrointestinal toxicity
- Enrolment in the AIR trial is completed and a global phase 2b trial to further evaluate the efficacy and safety of C21 in individuals with IPF (ASPIRE) is currently being developed.

