

Characterization of high responders in the phase 2a IPF AIR trial of C21 using baseline quantitative CT image analysis



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AIM: To find signals in historic CT scans that could identify patients more likely to respond to C21

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal disease of the lungs with a prevalence of 0.33-4.51 cases per 10,000 people¹. Fibrosis results in decline of lung function.

AIR is an ongoing phase 2a, multi-center, open-label, single-arm trial to evaluate the safety and efficacy of novel angiotensin II type 2 receptor agonist C21 for treatment of patients with IPF². Treatment is over 24 weeks, with an optional extension to 36 weeks.

Efficacy is assessed using Forced Vital Capacity (FVC) measurements. Results are compared to average untreated FVC decline of 60 ml per 12 weeks³.

Historic CT scans from up to 36 months prior to screening were collected for central reading.

Some patients with 36-week data show an improvement in FVC measurements. Here we characterize those patients using the historic CT scans, using interim data of 47 patients (16 with 24-week data).

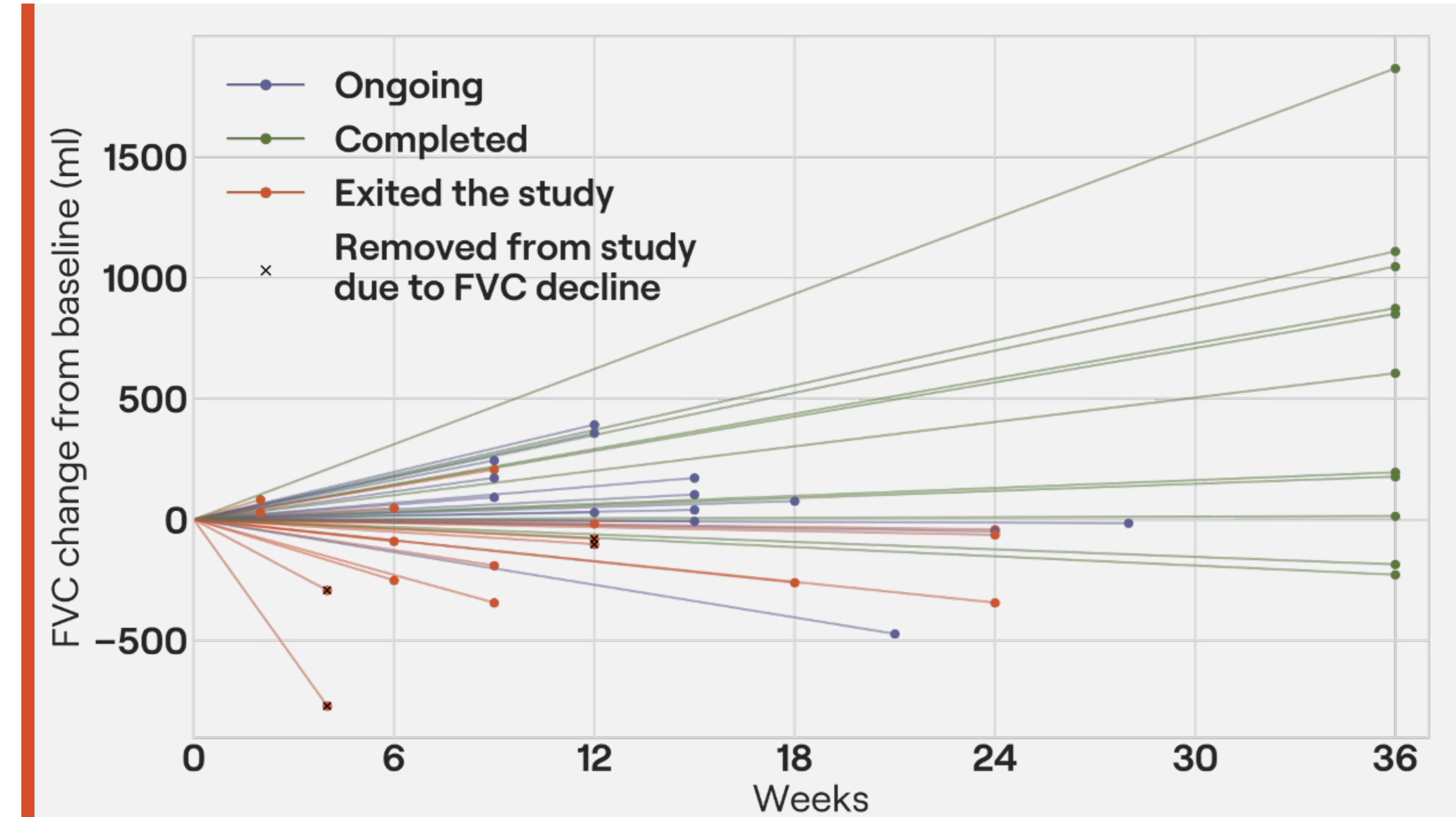


Figure 1. Change in FVC for each patient in the AIR trial, grouped by trial status, showing patients with improving FVC. Patients with significant decline from baseline in FVC twice consecutively and low FVC predicted were withdrawn from the study according to the trial protocol.

Methods

The Qureight platform enables automated segmentation of CT scans for volumetric quantification of lung, airway, vessel, and fibrosis volumes in the lungs of IPF patients. The models used are 3D Convolutional Neural Networks (CNNs) previously trained on IPF CT scans. All segmentation results underwent a QC check by a radiologist.

“High responders” are defined as patients with FVC percent predicted measurements that have improved at a rate of at least 10pp per year at either the 24- or 36-week endpoint.

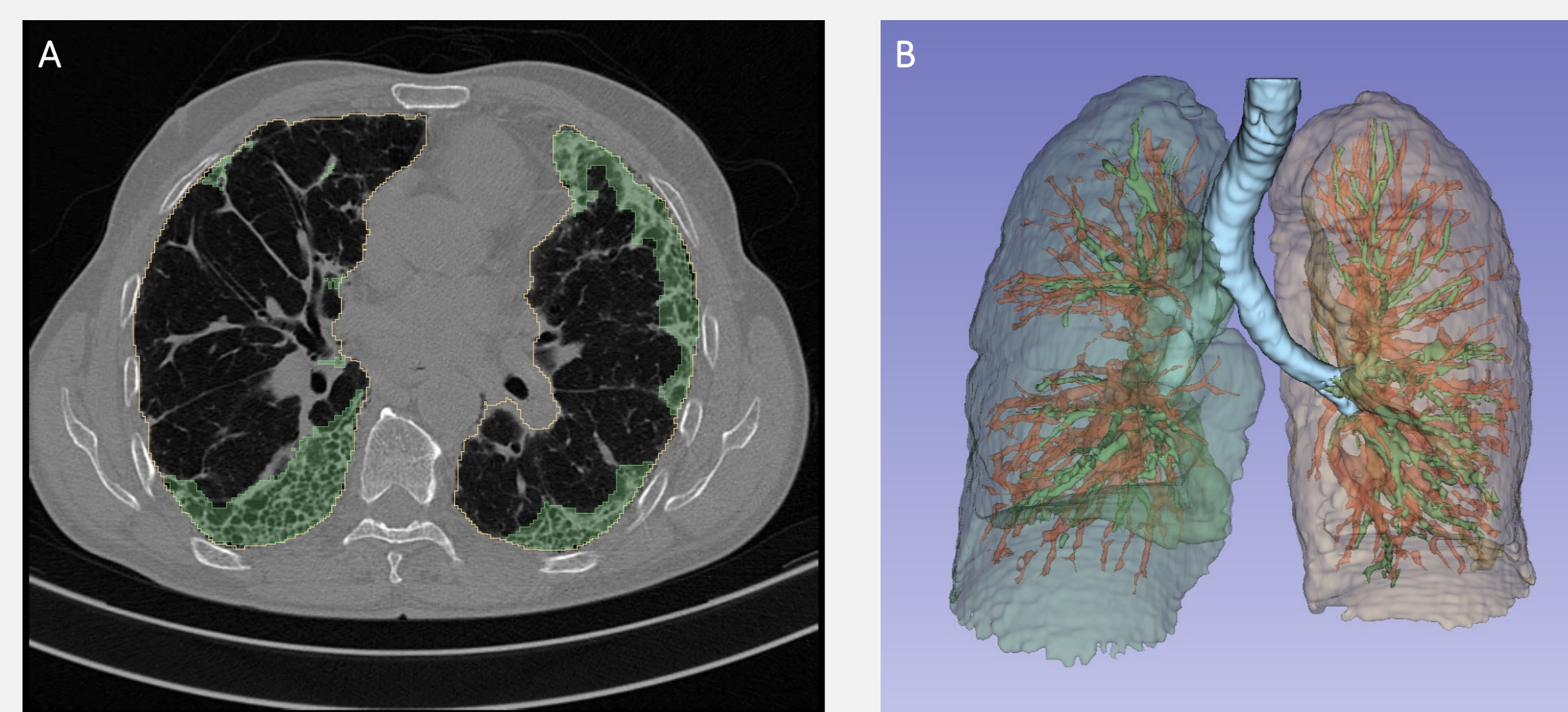


Figure 2. Automated segmentation of lung features by the Qureight platform. (A) shows segmentation of fibrosis. (B) shows a 3D render of the lung (transparent green/yellow), airway (blue/green), and vessel (red) segmentations.

Results: 24-week responders

Lung volumes, and normalized airway (excluding trachea), vessel, and fibrosis volumes are compared between high responders and the rest of the cohort.

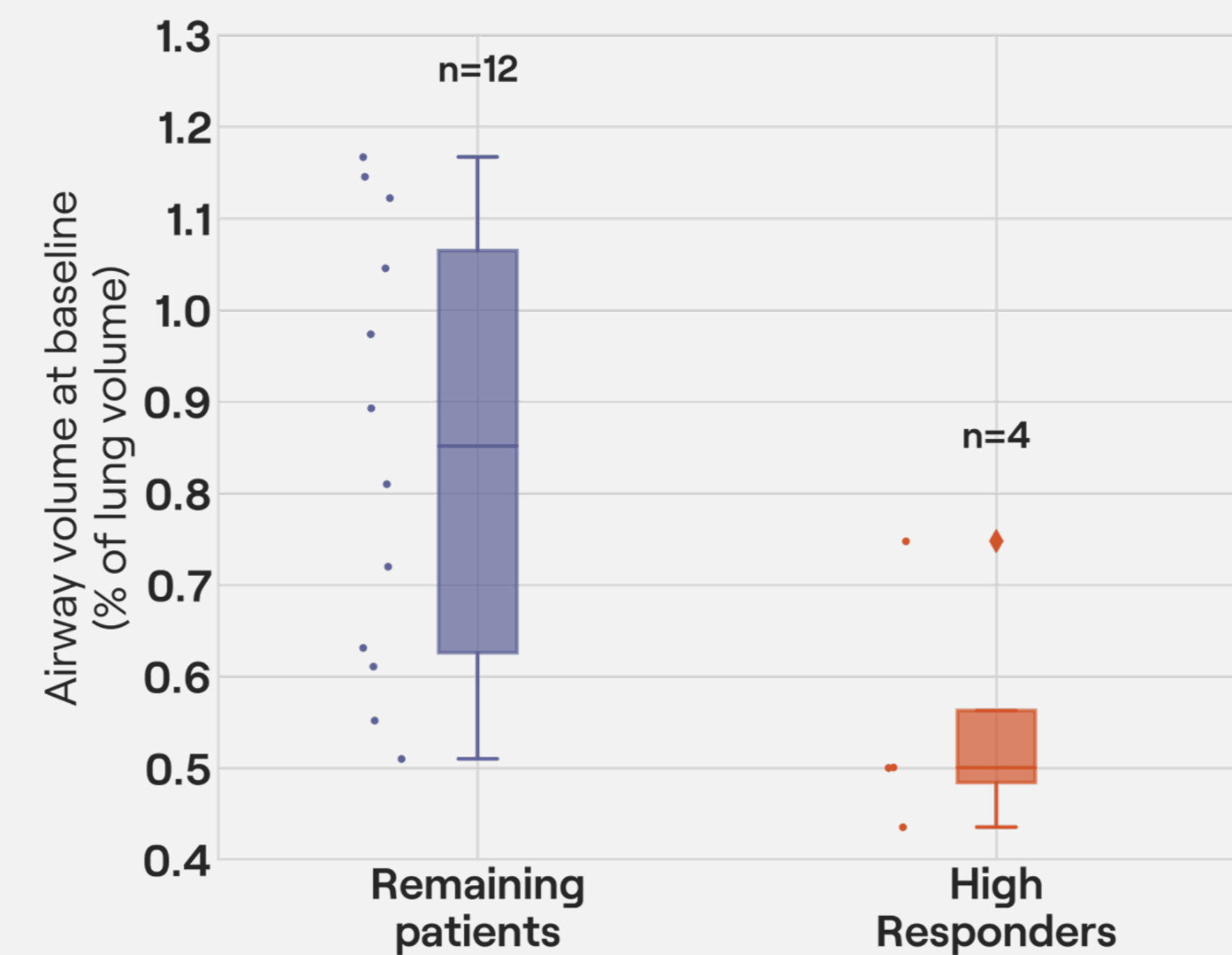


Figure 3. Normalized airway volume for patients at 24-week endpoint, showing difference between patients with improving FVC (high responders) and the rest of the cohort. Difference is significant – Mann Whitney p-value 0.02.

Table 1. Results from 24-week endpoint. Mann-Whitney Test (MW) is carried out when normality assumptions for ANOVA are broken. Airway volume difference is statistically significant and indicated with *.

Variable	High responder mean (s.d.)	Remaining cohort mean (s.d.)	Effect size (Cohen's d)	Statistical test	P-value
Lung volume (L)	3.36 (0.97)	3.58 (0.92)	0.24	MW	0.684
Airway volume (% of lung)	0.546 (0.14)	0.848 (0.24)	1.35	MW	0.0198*
Vessel volume (% of lung)	2.02 (0.14)	2.10 (0.32)	0.277	ANOVA	0.638
Fibrosis volume (% of lung)	15.3 (6.4)	15.1 (8.5)	-0.0248	ANOVA	0.966

Results: 36-week responders

There are no significant differences in vessel, airway, or fibrosis volumes between high responders and the rest of the cohort at 36-week endpoint.

However, all three volumes trend to lower values in the high responder group.

This could indicate lower disease severity in the responder group.

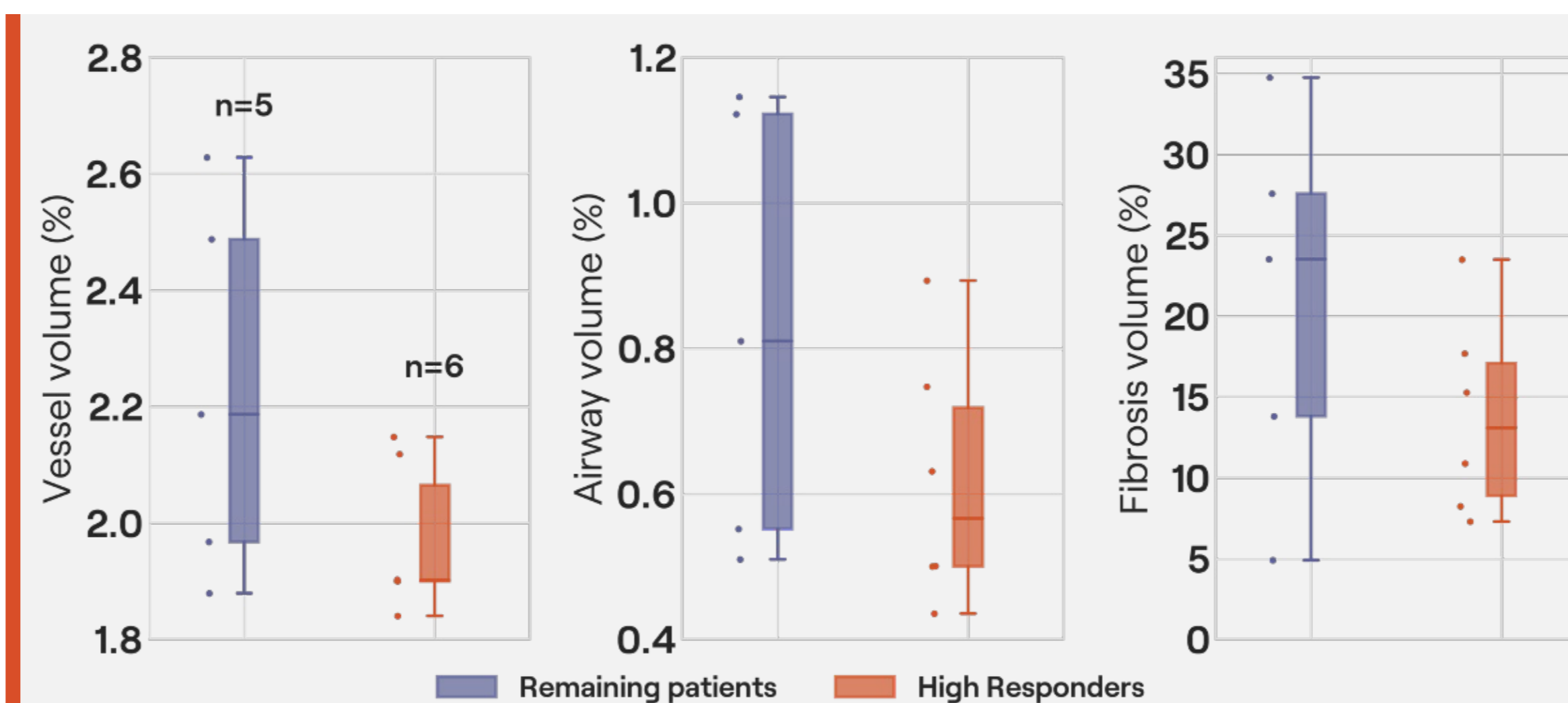


Figure 4. Comparison of normalized vessel, airway, and fibrosis volumes in patients with 36-week FVC data. Differences are not significant, but trend towards lower volumes in high responders.

Table 2. Results from 36-week endpoint. Mann-Whitney Test (MW) is carried out when normality assumptions for ANOVA are broken. No differences are statistically significant.

Variable (36 week)	High responder mean (s.d.)	Remaining cohort mean (s.d.)	Effect size (Cohen's d)	Statistical test	P-value
Lung volume (L)	3.19 (0.81)	3.07 (0.23)	-0.20	ANOVA	0.754
Airway volume (% of lung)	0.618 (0.18)	0.828 (0.30)	0.87	ANOVA	0.183
Vessel volume (% of lung)	1.97 (0.13)	2.23 (0.32)	1.10	MW	0.177
Fibrosis volume (% of lung)	13.2 (6.0)	20.1 (11)	0.78	ANOVA	0.229

Interpretation

Baseline FVC correlates well with lung volumes from historic CT scans. The Pearson correlation coefficient is 0.73.

This indicates that the CT scans are representative of baseline patient state.

Increases in airway volume due to traction bronchiectasis are associated with IPF progression and predict future mortality⁴. Increased pulmonary vessel volume is a predictor of functional deterioration⁵.

Patients with improving FVC had lower levels of IPF progression at baseline.

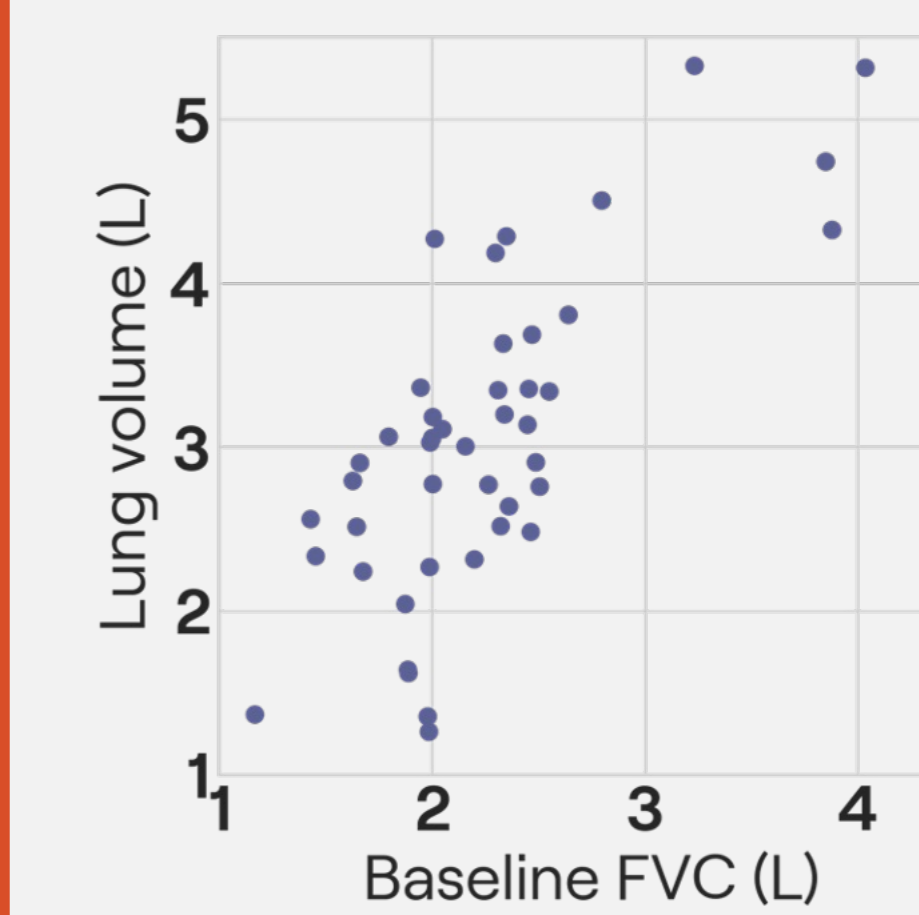


Figure 5. Baseline FVC measurements correlate well with lung volume obtained from historic CT scans.

Conclusions

- Automated quantitative analysis of historic CT scans can identify differences between patients with improving FVC measurements and the rest of the cohort in the AIR trial.
- Airway volumes are lower in high responders at the 24-week endpoint.
- Airway, vessel, and fibrosis volumes trend to lower values in high responders at the 36-week endpoint, but differences are not significant. These lower volumes are expected in individuals with less severe disease progression.
- This indicates that patients with less severe disease may respond better to C21.

References

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Conflicts of interest

Bussell, Thillai, and Ruggiero are employees of Qureight. Batta, Rosendahl, and Ganslandt are employees of Vicore Pharma. Bengtsson is a consultant to Vicore Pharma. Molyneaux and Maher have received advisory payments from Vicore Pharma and Qureight. The AIR trial is funded and sponsored by Vicore Pharma.