FVC variability in patients with idiopathic pulmonary fibrosis and role of 6-min walk test to predict further change

To the Editor:

Disease progression in idiopathic pulmonary fibrosis (IPF) is monitored by decline in forced vital capacity (FVC) [1]. An absolute or relative decline in % predicted FVC ⩾10% is associated with mortality [2, 3]. Measures of FVC decline were selected as primary endpoints in the pivotal phase 3 trials of antifibrotic therapies [4–6]. Despite consistent trends for FVC decline in the IPF population, the rate of disease progression in individuals is unpredictable and highly variable: significant variability in FVC is observed over time, and prior declines are a poor predictor of future FVC decline [1, 7, 8]. In new trials in IPF, the margin for reducing FVC decline is smaller (∼70 mL) in patients who are receiving an investigational drug with background antifibrotics than in the placebo arms of past trials (130–210 mL) [9].

Considering additional clinical variables in trial endpoints may provide the ability to identify small changes in FVC that represent disease progression. The objectives of this *post hoc* analysis of data from patients with IPF enrolled in phase 3 clinical trials were to examine the variability in FVC (mL) across 3-month follow-up visits and, using 6-min walk distance (6MWD), to explore whether combined clinical measures can more accurately predict disease progression than short-term changes in FVC alone.

Patients randomised to receive placebo in ASCEND (study 016; NCT01366209) and CAPACITY (studies 004 and 006; NCT00287716 and NCT00287729) and all patients randomised to receive interferon-γ-1b or placebo in GIPF-001 (NCT00047645) were included [4, 5, 10]. Eligibility criteria were previously described [4, 5, 10]. Data from all trials were included to evaluate the first objective in a broader IPF population. However, only data from ASCEND and CAPACITY were included to evaluate the second objective because 6MWD was not captured in GIPF-001.

Spirometry tests were performed every 3 months for 52–72 weeks [4, 5, 10]. Tests were performed in accordance with the 2005 American Thoracic Society (ATS) manual in ASCEND and CAPACITY and the 1987 ATS standardisation in GIPF-001 [11, 12]. Pre-bronchodilator FVC values used in this analysis were: the best effort (or maximum acceptable effort if best effort was unavailable; from at least three measurements) from ASCEND, the maximum recorded (from at least three measurements) from CAPACITY and the value reported on the case report form from GIPF-001.

Changes in pre-bronchodilator FVC (mL) in individuals were calculated as the difference between measurements at the first and second visits of each 3-month interval (*e.g.* baseline to month 3, month 3 to month 6). The probability of further change in FVC after an initial 3-month relative decline (2% decrements) was calculated for the subsequent 3-month interval. The role of the 6MWD in validating these small relative changes (2% decrements) in FVC was assessed in data from ASCEND and CAPACITY. Concurrent 3-month change in 6MWD was categorised as decreased (⩽−5% of initial value), stable (>−5% to <5%) or improved (⩾5%). The probability of further change in FVC in the subsequent 3 months after an initial 3-month relative decline in FVC was categorised by both the initial relative decline in FVC and concurrent change in 6MWD. The probability of ⩽−10% relative change in FVC over 6 months was estimated by identifying combinations of initial and subsequent 3-month change categories that indicated patients had ⩽−10% total change. Only initial intervals with declines in FVC and consecutive 3-month intervals were considered. FVC decrements of 2% and 5% change in 6MWD were

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Variability in 3-month changes in FVC was examined in 954 patients with IPF (n=3966 observations) from phase 3 trials; concurrent 3-month decline in the FVC and 6MWD (n=1321 observations) predicted further decline in FVC over the subsequent 3 months http://bit.ly/2GfBKW3

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selected to yield a sufficient number of events for analysis and to explore whether changes that are smaller than the typically recognised minimal clinically important differences, when considered together, might provide insight into disease progression.

A total of 954 patients were analysed. In ASCEND and CAPACITY, 624 patients received placebo [4, 5]. In GIPF-001, 168 patients received placebo, and 162 received interferon-γ-1b. At baseline, mean % predicted FVC and % predicted diffusing capacity for carbon monoxide (D_{LCO}) were lower in GIPF-001 than in ASCEND and CAPACITY (FVC, 64% *versus* 72%; D_{LCO}, 37% *versus* 46%). More patients had supplemental oxygen use at baseline in GIPF-001 than in ASCEND and CAPACITY (36% *versus* 24%).

Across 3966 observations, 41.3% of 3-month changes in FVC (mL) were stable or improved (⩾0 mL), and 58.7% were declines (<0 mL). Nearly 50% of 3-month intervals showed a change of ⩾100 mL (decrease or increase). Consistent with published findings for longer time intervals, a relative decline in FVC over 3 months was a poor predictor of further decline in the subsequent 3 months [7, 8].

The hypothesis that a 3-month relative decline in FVC (mL) accompanied by a concurrent decrease in 6MWD could predict whether a patient would have a total relative decline in FVC ⩾10% over 6 months was explored (table 1). Changes in 6MWD concurrent with a small initial relative decline in FVC over 3 months (<0% to ⩾−2%) were not predictive of subsequent relative decline in FVC. However, larger initial 3-month relative declines were more likely to result in a total relative decline in FVC over 6 months of ⩾10% (change, ⩽−10%) when accompanied by a concurrent decrease in 6MWD. The probability of a total 6-month relative change in FVC of ⩽−10% approximately doubled with each 2% decrement in initial 3-month relative change in FVC in patients with an initial 3-month decrease (⩽−5%). For example, the likelihood of a total 6-month relative change in FVC of ⩽−10% was greater in patients with an initial 3-month relative change in FVC of <−6% to ⩾−8% than in those with an initial change of <−4% to ⩾−6% (32.8% *versus* 17.3%).

As demonstrated by our analysis, additional measures of disease progression could validate small declines in FVC as clinically meaningful and, thus, enrich the number of patients with IPF who meet a clinical trial endpoint. 6MWD independently predicts mortality in patients with IPF and appears useful in concert with FVC decline [13]. It is important to recognise that other sources of variability in FVC measurements should be considered in both clinical practice and when designing trials with FVC as an endpoint. With optimal quality control, the accuracy of spirometry equipment should be ±2.5% [14]. Patient effort, test performance, test result selection, number of measurements, changes in disease state and comorbid conditions, such as respiratory tract infections, can impact spirometry test results across visits [14]. Age-related FVC decline (~30–35 mL per year in healthy adults aged 60–80 years), while less than FVC decline due to IPF progression, might affect measurements of change [15]. Changes in dyspnoea or increased supplemental oxygen use could also potentially discern whether a small decline in FVC represents disease progression.

TABLE 1 Relative change in forced vital capacity (FVC) (mL) over 3 months as a predictor of estimated 6-month relative change in FVC (mL) ⩽−10% and the role of 6-min walk distance (6MWD) in improving the prediction in patients with idiopathic pulmonary fibrosis[#]

Initial 3-month relative change in FVC (mL), %	Probability of total 6-month relative change in FVC (mL) ⩽−10%, %[¶]			
	All observations[+]	Decreased 6MWD (initial 3-month relative change ⩽−5%)	Stable 6MWD (initial 3-month relative change >−5% to <5%)	Improved 6MWD (initial 3-month relative change ⩾5%)
<0 to ⩾−2	3.8	6.5	3.3	1.6
<−2 to ⩾−4	9.0	9.4	10.3	5.3
<−4 to ⩾−6	10.5	17.3	8.9	5.6
<−6 to ⩾−8	27.2	32.8	25.4	17.6
<−8 to ⩾−10	36.5	44.7	38.5	20.8

[#]: observations from patients with idiopathic pulmonary fibrosis who had ⩾1 occurrence of relative decline in FVC (mL) over 3 months among those who were randomised to receive placebo in ASCEND and CAPACITY. [¶]: probabilities were based on the occurrence of consecutive 3-month changes in which the upper boundary of change categories summed to ⩽−10%. For example, a patient with an initial 3-month relative change of <−4% to ⩾−6% who had a subsequent 3-month relative change of ⩽−6% would have a total decline for the 6-month interval of ⩾10% (relative change, ⩽−10%). Only initial intervals with declines and consecutive 3-month intervals were considered. Cases were not counted if the upper boundary of consecutive 3-month change categories did not sum to ⩽−10%, even if the actual consecutive 3-month changes could have indicated a ⩽−10% relative change in FVC (mL). [+]: probability of total 6-month relative change in FVC (mL) ⩽−10% using all available observations regardless of initial 3-month relative change in 6MWD.

This *post hoc* analysis has several limitations. Only patients who received placebo were examined in the FVC–6MWD analysis but not those receiving antifibrotics. Whether FVC and 6MWD changes would complement one another in patients with IPF receiving antifibrotics is therefore uncertain. Age and comorbidities, which influence lung function, were not assessed. Clinical trial data may not reflect real-world experience. Importantly, observed 3-month changes in FVC might reflect visit-to-visit variability, disease progression or both. The correlation between repeated FVC measurements within the same subject was not explicitly considered in the analysis; however, this potential correlation should negatively affect the variability calculation (*i.e.* diminish the variability) instead of positively inflating it. Due to the lack of independence among all observations, precision of estimates was not calculated. In some cases, the estimates were based on a relatively small number of observations (<40) due to the observed combinations of initial FVC and 6MWD changes. Therefore, these results should be interpreted with caution and ideally investigated in another population.

In summary, this analysis examined FVC variability at 3-month intervals in a large well-characterised cohort of patients with IPF. Concurrent analysis of 3-month change in FVC (mL) and 6MWD might allow the prediction of ⩾10% relative decline in FVC over 6 months, especially when both FVC and 6MWD are decreased. This analysis could inform both clinical practice and the design of new endpoints for clinical trials in IPF.

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Qualified researchers may request access to individual patient–level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx Further details on Roche's Global Policy on the Sharing of Clinical Study Information and how to request access to related clinical study documents can be found at www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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