

THE ASSOCIATION OF DEMOGRAPHIC AND PHYSIOLOGICAL
VARIABLES AND RISK OF SUBSEQUENT DISEASE PROGRESSION IN
IDIOPATHIC PULMONARY FIBROSIS

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Abstract

**The Association of Demographic and Physiological Variables and Risk of
Subsequent Disease Progression in idiopathic Pulmonary Fibrosis**

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Background. Efficient clinical trial design in idiopathic pulmonary fibrosis (IPF) is hindered by incomplete understanding of the natural history of IPF and absence of robust predictive models. A retrospective analysis of the RAINIER clinical trial for simtuzumab, an inhibitor of lysyl-oxidase-like-2 (LOXL-2), was conducted to identify clinically predictive variables associated with IPF disease progression. The RAINIER trial was discontinued for lack of efficacy. Because the trial did not demonstrate efficacy, it was considered appropriate to include both control and simtuzumab treated subjects.

Methods. RAINIER was a randomized, double-blind, phase 2 clinical trial (NCT01769196) conducted at 181 respiratory clinics in 14 countries. Patients with IPF diagnosed within 3 years prior to screening or with evidence of clinical worsening were enrolled between March 2013 and June 2015 and randomized 1:1 to simtuzumab or placebo. Standard demographic and physiological baseline variables, 2 baseline exploratory endpoints (serum LOXL2 and fibrosis score from quantitative high-resolution computed tomography and the change in forced vital capacity (L) over 14

weeks (prodromal Δ FVC) from placebo-treated patients, were used to generate predictive models for weeks 14–66 for change in forced vital capacity (FVC), time to disease progression (as a composite of mortality and categorical decrease in FVC), death, and time to first all-cause and adjudicated respiratory hospitalization. A backward process selected variables (threshold $p \leq 0.05$) using a linear mixed model for Δ FVC. A stepwise process selected variables (entry threshold $p = 0.10$, stay threshold $p = 0.05$) in survival analysis for time-to-event outcomes. Performance of the predicted models was evaluated by a 10-fold cross-validation method.

Results. Of 544 subjects enrolled in the study, 501 remained in the study at 14 weeks. An increased prodromal Δ FVC was associated with increased risk for decreased time to death, (HR=0.936, $p=0.017$, first adjudicated respiratory hospitalization (HR=0.980, $p=0.001$) and categorically defined disease progression (HR =0.936, $p < 0.0001$) over 52 weeks but was paradoxically associated with a reduced rate of decline in FVC over the same period (Pearson correlation coefficient [R] = -0.2060, $p < 0.001$). Prodromal Δ FVC was not significant in the model of time to death or all-cause hospitalization. Serum LOXL2 at baseline significant predictor of mortality but not of other endpoints

Conclusion. In a well-characterized clinical trial population, an increased rate of prodromal decline in FVC was associated with an increased risk of respiratory death, hospitalization and categorically defined disease progression, but was not associated with an increased rate of subsequent FVC decline over the subsequent 52 weeks.

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DEDICATION

This thesis is dedicated to my wife Caroline.

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This is a post hoc analysis of a clinical trial. The original clinical trial is registered on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01769196) (NCT01769196) and the topline results of pre specified efficacy and safety data are accepted for publication in Lancet Respiratory Medicine.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fatal interstitial lung disease with its highest prevalence in elderly males with a history of tobacco use. (Raghu, 2011). Despite the recent approval of two medications, pirfenidone and nintedanib, that can reduce the rate of decline in lung function (Karimi-Shah, King, Richeldi 2014), there is agreement that novel medications that are more effective and better tolerated are urgently required to adequately manage this disease (Raghu, 2015). The development of novel medications faces significant challenges including an incomplete understanding of pathogenesis and the absence of efficient clinical trial designs to evaluate candidate compounds (Blackwell, Collard, O’Riordan)

Efficacy endpoints in clinical trials in IPF, are usually either change in forced vital capacity (FVC) measured as a continuous variable over at least 12 months or a composite event of clinically relevant events that would indicate progression of disease (such as time to categorical decrease in FVC, death, hospitalizations, lung transplant etc.) (Karimi-Shah, Collard). Due to heterogeneity in rates of disease progression, data from several hundred subjects, treated over at least 12 months are required to obtain robust initial evidence of efficacy (Richeldi 2011, O’Riordan)

Analyses of data from real world clinical data bases (Reichman, Salisbury 2016a, Schmidt) and clinical trial datasets (Ley 2012, 2015, 2016) have been undertaken to enable more efficient trial design and to gain a more precise appreciation of the natural history of IPF. These analyses have identified baseline physiological and demographic associated with increased risk of mortality, most notably the Gender Age and Physiology (GAP) Index (Ley, 2012). Even though the GAP index was validated in both real world and clinical data bases, the Index tends to overestimate mortality in the latter (Lay 2015). The most likely explanation is that the eligibility criteria used in clinical trials relating to clinical stability and comorbidities select populations at lower risk of mortality. Conversely, nonintervention observational trials in IPF which tend to be more inclusive than interventional trials, may have higher mortality than the latter (Jenkins).

In an effort to increase the precision of predictive model in clinical trial cohort selected from the pirfenidone and interferon gamma clinical trial databases, incorporation of 24-week prodromal longitudinal data on respiratory hospitalizations and rate of change in FVC, was found to significantly increase the predictive accuracy of the GAP model for mortality over the subsequent 52 weeks (Ley 2015). However subsequently, when clinical models, including prodromal change in FVC over 24 weeks, were applied to longitudinal premortality disease progression (including change in FVC over subsequent 52 weeks) the models which were predictive of mortality failed to meaningfully predict outcomes (Ley 2016).

The poor predictive value of prodromal rate of decline in FVC with subsequent decline in FVC in a clinical population was consistent with findings of multiyear analyses of real world clinical data bases (Salisbury and Schmidt). These results were especially disappointing because longitudinal change in FVC was the primary endpoint in the registration trials of nintedanib and pirfenidone (Karimi-Shah, King, Richeldi 2014)

In the present study, we analyze data from a clinical trial of simtuzumab that was terminated for lack of efficacy (Raghu, 2016 b). Simtuzumab is a monoclonal antibody that inhibits lysyl oxidase like 2 (LOXL2), an enzyme that cross links collagen, an important step in creating the fibrotic matrix (Barry-Hamilton). Predictive models for clinically relevant outcomes were generated using baseline variables combined with longitudinal change the change in FVC, diffusion capacity for carbon monoxide (DLCO), 6 minute walk distance (6MWD) and St George's Respiratory Questionnaire (SGRQ)_over the first 14 weeks to predict change in FVC over the subsequent 52 weeks. The study population and evaluations had some unique features. The trial population was enriched for subjects with more impaired baseline lung function relative to other large clinical trials. Subjects with respiratory hospitalizations within prior 24 weeks were excluded because that factor was known to be associated with increased mortality (du Bois). The FVC was measured at 4 weekly intervals instead of 12 weeks/3 months in most other trials (Noble 2011. Raghu 2013, Richeldi, 2014) All available hospitalization and death clinical data were reviewed in a blinded manner by an expert panel to

adjudicate the cause of these events, instead of relying on local investigators to assign causality. Finally, with the advent of antifibrotic therapies as standard of care (Raghu 2014) , this is likely to be the last global trial in IPF to include subjects randomized to a true placebo arm, making this data set especially valuable for evaluating the natural history of the untreated disease (Collard 2016, O'Riordan).

METHODS

This is a post hoc analysis of the results of a placebo-controlled parallel group stratified, multicenter study from March 2011 until the study was prematurely terminated in January 2016. The Sponsor terminated the study after an independent Data Monitoring Committee (DMC) had reviewed results of a prespecified interim analysis and proceeded to advise that the study be terminated on the grounds of lack of efficacy. The Sponsor accepted the recommendation of the DMC and stopped the trial.

The study was stratified based on 3 levels of forced vital capacity FVC (> 75-90 % predicted, 55-75% predicted, < 55%); and 3 levels of baseline serum LOXL2 (below limit of quantification, <800 IU/ml, \geq 800 IU/ml). The rationale for stratification based on FVC was based on evidence from prior studies that increasing severity of baseline FVC impairment was associated affected with increased mortality risk (du Bois). The rationale for stratification based on LOXL2 levels was based an earlier retrospective analysts that had reported that LOXL2 levels had prognostic significance with elevated levels associated with increased risk of disease progression or death. (Chien)

The study population

The study was conducted at 180 sites in 14 countries (USA, Canada, United Kingdom, France, Belgium, Germany, Poland, Czech Republic, Switzerland, Italy, Spain, Israel, Australia, South Korea).The key inclusion and exclusion criteria included the following

1. Male and female subjects aged between 45 years and 85 years
2. The diagnosis of IPF consistent with the 2011 American Thoracic Society/European Respiratory Society diagnostic criteria and verified by centralized review of high resolution computed tomography (HRCT) and if

- available, of surgical lung biopsies. In addition, the subjects with significant emphysema on HRCT review were excluded HRCT
3. The diagnosis of IPF should have been established within 3 years of enrollment in the study. However subjects with a longer established diagnosis could be enrolled if there was evidence of disease progression in the preceding 12 months.
 4. The baseline FVC could not exceed 90% of predicted but there was now lower limit of this value
 5. The baseline diffusion capacity for carbon monoxide corrected for hemoglobin could not be less than 25% predicted.
 6. Lung function testing could not show evidence of airway obstruction (forced expiratory volume in one second/force expiratory volume (FEV₁/FVC) less than lower limit of normal for age
 7. While, the use of supplemental oxygen during sleep or exercise was permitted, the resting oxygen saturation at rest breathing room air had to be at least 88%
 8. Subjects with acute respiratory hospitalizations within 24 weeks of enrollment excluded except for cases discussed with medical monitor which the indication for admission had resolved to the satisfaction of the medical monitor.
 9. Subjects with significant concomitant diseases including unstable cardiovascular disease or neoplastic disease, were excluded

Regulatory approval and informed consent.

The study protocol was submitted as part of an Investigational New Drug (IND) application to the US Food and Drug Administration, and approval was also obtained from Canada, European Medicines Agency, in association the relevant Individual European national regulatory authorities in United Kingdom, France, Belgium, Germany, Poland, Czech Republic, Italy, and Spain. Spate approvals were obtained from national authorities in Canada, Switzerland Israel, Australia, and South Korea. At each site, the study was approved by an Institutional Review Board or Ethics Committee and informed written consent forms were approved at each site. The Sponsor engaged an international clinical research organization to undertake monitoring visits to all sites to ensure adherence to Good Clinical Practice guidelines. The study was registered at Clintrials.gov

(NCT01769196)

Confidentiality.

Each study subject was assigned an individual clinical trial participant number which also included number the study site. However the subjects' unique identifying information was not provided to the sponsor. The data analysis performed for this post hoc analysis was therefore performed on de-identified data.

Primary Endpoint,

There were three primary endpoints: progression-free survival (PFS) in the intent to treat group and progression-free survival in two serum "LOXL-2 High" sub groups. "LOXL-2 High" was predefined as the subjects with greater than the median level of serum OXL2 at baseline and in another group as greater than the 75th percentile. Progression Free Survival defined as time to: (a) death from any cause or (b) $\geq 10\%$ relative decline in FVC from baseline AND $\geq 5\%$ absolute change

Course of the study

The study design was event-driven but patients were encouraged to remain in the study on blinded therapy even if they had met spirometric disease progression. The trial was initiated prior to the US Food and Drugs administration (FDA) approval of pirfenidone and nintedanib and is therefore likely to one of the last large trials to include a true placebo arm.

The course of the study was complicated by the approval of two new medications pirfenidone and nintedanib. It became apparent that a placebo controlled trial that excluded approved therapies would not be feasible or permissible. Therefore an Amendment was introduced The study protocol was modified to permit either stratified entry of subject's already on pirfenidone or nintedanib or to allow initiation of these agents after randomization.

The study was fully enrolled with 543 subjects as of July 2015. In late September the

200th PFS event occurred and a data set was prepared for the intent DMC futility analysis. The DMC met on December 23 and advised termination due to lack of efficacy. On January 2, 2016, having reviewed the DMC recommendation, the Sponsor announced the termination. Study medication was terminated and final visits arranged with 30 days. The final data base was locked May 11, 2016.

Evaluations

The FVC was measured using centralized spirometry at 4-weekly intervals, with more detailed assessments with 12 weeks, including diffusion capacity for carbon monoxide (DLCO), 6 minute walk distance (6MWD) and St Georges Respiratory Questionnaire (SGRQ). The 6 minute walk test was performed using ATS standards. Subjects could use up to 6 liter of supplemental oxygen during the study but the amount of then had to be constant at all tests. If a subject was unable to participate in the study with an incremental increase in supplemental oxygen, a value of zero was entered.

Hospitalizations

Hospitalizations were adjudicated in a blinded manner by an expert committee, as: a) non-respiratory cause, b) definite acute exacerbation of IPF (AEIPF), c) suspected AEIPF, d) alternative respiratory etiologies, and d) unclassifiable. The same committee also adjudicated all deaths that occurred in the study.

Statistics

Baseline demographic and physiological factors (were selected based on the published literature of IPF: age, body mass index (BMI) smoking status (ever versus never, Region (North America versus Europe versus Asia-Pacific), duration of IPF diagnosis, FVC, residual volume (RV), DLCO % predicted, 6MWD in meters and SGRQ. For FVC the value at week 14 was used instead of the baseline value.. These factors were included in a multivariate analysis of disease outcome from week 14 to 66 of the study along with two exploratory variables, the fibrosis score on HRCT and the serum LOXL2. Treatment (placebo or simtuzumab) was also included. In addition to the baseline variables, change

in four longitudinal variables (FVC, DLCO % predicted, SGRQ and 6MWD) over a prodromal period (weeks 0 to 14 weeks) were included in the model.

A backward process selected variables (threshold $p \leq 0.05$) using a linear mixed model for the continuous outcome Δ FVC. A stepwise process selected variables (both entry and stay threshold $p = 0.05$) in survival analysis for time-to-event outcomes. Performance of the predicted models was evaluated by a 10-fold cross-validation method in which the study population was divided randomly into 10 equal subgroups. The model was trained on 9 of these subgroups and then applied to the remaining subgroup to obtain their prediction and comparing those predictions to their observed counterparts. Predictive accuracy was measured by the $\sqrt{\text{MSE}}$, the prediction standard error, for continuous outcomes (Δ FVC) (Armstrong) and the C-index for prediction concordance for time-to-event outcomes (Ley 2016). The C-Index can have values from zero to one, with values of 0.7 or above considered to have good discriminant value between the occurrence and nonoccurrence of the binary outcome. In the present analysis the $\sqrt{\text{MSE}}$ has values between 0 and 1, with lower values indicating better predictive accuracy than higher values.

Pearson correlation coefficients were calculated in univariate analysis of the relationship of baseline variables to change in Δ FVC from weeks 14-66.

RESULTS

Of 544 subjects enrolled in the placebo arm, 501 remained in the study at 14 weeks. Baseline characteristics are summarized in Table 1. The mean (SD) age was 68.1 (7.3) years, 83% were male and 71% were ex-smokers. Forty-three (43) % were enrolled in North America, 39% in Europe and 18% in Asia/Pacific. The mean (SD) percent predicted values of the FVC and DLCO were 62 (12) and 38 (11) respectively. 15% of the population had been on pirfenidone at time of enrollment.

The key results of the models are shown in Tables 2-4 for the 52 week period between week 14 and week 66. Table 2 shows the model for change in FVC as a

continuous variable Table 3 shows the models for categorical disease progression and death. Table 4 shows the model for time to first all cause hospitalization and first adjudicated respiratory hospitalization.

An increased prodromal Δ FVC was associated with increased risk for decreased time to death, (HR=0.936, p=0.017, first adjudicated respiratory hospitalization (HR=0.980, p=0.001) and categorically defined disease progression (HR =0.936, p< 0.0001) over 52 weeks but was paradoxically associated with a reduced rate of decline in FVC over the same period (Pearson correlation coefficient [R] =---2.060, p<0.001). Prodromal Δ FVC was not significant in the model of time to first all-cause hospitalization (HR =0.999, p=0.773).

.Decreased FVC was associated with increased risk of disease progression (HR=0.998 and p =0.043) but no significant association was observed with the other three binary outcomes. For the continuous variable of change in FVC over 52 weeks (Δ FVC 14-66), the degree of impairment measured at FVC% predicted at week 14, the “reset baseline”, was associated with a reduced rate of subsequent decline in FVC ((Δ FVC 14–66). In contrast, the baseline residual volume (RV% predicted) was associated with a more rapid change in the Δ FVC 14-66.

An increase in the FEV₁/FVC ratio was associated with increased risk of death, disease progression, and all cause hospitalization and adjudicated respiratory hospitalization. Impairment of baseline DLCO % predicted corrected for hemoglobin was associated with increased risk of death ((HR=0.95, , p=0.006), all cause hospitalization (HR=0.974, p=0.012) adjudicated respiratory hospitalization (HR 0.948, p < 0.0001) but not disease progression. More severe impairment of baseline health related quality of life (HRQoL) as measured by increased baseline St Georges Respiratory Questionnaire (SGRQ) was associated with increased risk of all cause hospitalization (HR 1.015, p= 0.002) and risk of adjudicated respiratory hospitalization (HR=1.021, p< 0.001) Worsening of respiratory symptoms (as

measured by increasing SGRQ score) was associated with more rapid decline over subsequent 52 weeks.(R=0.0002, p=0.005)

An increase in baseline HRCT fibrosis score was associated with increased risk of categorical disease progression (time to PFS event, HR=1.022, p< 0.0010.), decreased time to first all-cause hospitalization (HR=1.023, p=0.003) and increased rate of subsequent decline in FVC over 52 weeks (Pearson R =-0.002, p=0.015).

Other significant association between baseline factors and outcomes included increased BMI and increased risk of first hospitalization (HR= 0.949 and p=0.014) and longer duration of IPF diagnosis was associated with reduced risk of death (Log IPF diagnosis duration, HR=0.633, p=0.029). Serum LOXL2 at baseline was associated with increased risk of death (HR=2.961, p=0.013) Study treatment (simtuzumab versus placebo) was not significant in any of the models evaluated.

The C-indexes for the binary endpoint predictive models were 0.64 for time to death, 0.69 for time to disease progression. 0.76 for time to first all cause hospitalization and 0.72 for time to first adjudicated respiratory hospitalization. For the predictive model of the continuous endpoint of change in FVC over 52 weeks, the $\sqrt{\text{MSE}}$ was 0.211

Univariate analyses of relationship of the individual baseline variables to change in FVC over weeks 14 to 66 are shown in Table and none reached statistical significance (Table 5). A univariate analysis of the risk associated with an increase in Gender Age Physiology Index for risk of death from any cause showed a p value of 0.0087

DISCUSSION

In a well-defined clinical trial population of patients with idiopathic pulmonary fibrosis (IPF) an increased prodromal rate of decline over 14 weeks in forced vital capacity (ΔFVC 0-14 weeks) was associated with shortened time to clinically significant events

(adjudicated respiratory hospitalizations and decreased progression free survival as defined by death or categorical decrease in FVC) but was paradoxically associated with more rapid prodromal decline in FVC and was associated with a decreased rate of FVC decline over the subsequent 52 weeks (Δ FVC 14-66 weeks). Increased Δ FVC 0-14 weeks was not significant in the model of time to death or all-cause hospitalization.

These findings complement those of a recent retrospective analysis from clinical trials of pirfenidone and gamma interferon (Ley 2016). The latter found that predictive models that combined decline in FVC over the first 24 weeks with standard cross sectional demographic and physiological variables at week 24, were not useful in predicting decline in FVC and other continuous physiological outcomes over the subsequent 52 weeks. The same group had previously analyzed the impact of a 24 week longitudinal prodromal data on prediction of mortality in the same dataset and found that prodromal respiratory hospitalizations enhanced the predictive value of the Gender Age Physiological Index, which is composed of baseline cross sectional variables (age gender FVC and DLCO).

There are potentially important differences between the population in the current study and the population in the pirfenidone/interferon analysis (Ley 2016). The current study (RAINIER) excluded subjects with respiratory hospitalizations within the prior 24 weeks because that factor was known to be associated with increased mortality (duBois). The current study had enrolled subjects with more severe baseline impairment of FVC and DLCO than the pirfenidone/interferon population. Thus even though the current population had been enriched for impaired baseline lung function, the exclusion of recent respiratory hospitalizations may have decreased overall mortality risk. Nevertheless despite the relatively low death rate of 6%, increasing GAP stage was significantly associated with increased risk of mortality.

The finding that a rapid decline in prodromal FVC is not associated with subsequent rapid decline complement findings in real world retrospective analyses of the predictive value of lung function (Schmidt). Schmidt et al found that more rapid decline in FVC

over one year was associated with increase of death over the subsequent 24 months but was a poor predictor of subsequent linear decline in lung function. These results complement results of earlier analyses of clinical trial data sets (Richeldi 2012) and real world data sets (Reichman) that categorical decline in FVC is associated with a subsequent increased risk of mortality. Prodromal worsening of respiratory symptoms as measured by SGRQ is associated with increased risk of decline in FVC over subsequent 52 weeks.

Hospitalizations are a potentially useful endpoint in clinical trials (Collard 2014). In this present analysis all-cause time to hospitalizations and adjudicated respiratory hospitalizations were endpoints of clinical interest. It is important to acutely distinguish respiratory from non-respiratory hospitalizations in IPF because the former but not the latter have been reported as associated with increased risk of death in an analysis of clinical trial data (Durheim). In the RAINIER study over half of the hospitalizations were adjudicated as being not due to non-respiratory causes (Raghu 2016). Prodromal decline in FVC (Δ FVC Week 0-14,) was selected for the model for time to first adjudicated respiratory hospitalization but not the model for time to first all-cause hospitalization. Both hospitalization models selected DLCO % predicted, and SGRQ as significant associations. In all four models with binary outcomes, an increase in FEV₁/FVC ratio was associated with increased risk of occurrence of these clinically significant events. An increase in the FEV₁/FVC ratio could be viewed as a surrogate for increase elastic recoil in IPF, suggestive of more severe fibrosis.

Two novel biomarkers were evaluated in the baseline model, a fibrosis score based on the HRCT and the serum LOXL2. An increase in baseline HRCT fibrosis score was associated with increased risk of categorical disease progression and time to first all cause hospitalization and with increased rate of subsequent decline in FVC. . This finding complements the recent finding by Salisbury et al in a clinical trial population that severity of baseline quantitative on HRCT score is associated with increased risk of disease progression (defined as categorical decrease in FVC, death or hospitalization). In a prior publication, LOXL2 levels showed promise as a

predictive biomarker (Chien) for death and disease progression... In the present study, while there is an association between risk of death and high levels (Log (LOXL2), this variable was not selected for the other outcomes. This outcome shows the importance of validating a promising biomarker in retrospective studies in large prospective studies using well characterized assays.

In conclusion, analysis of the data from a clinical trial population enriched for baseline impairment of FVC shows a more rapid prodromal decrease in FVC over 14 weeks. Prodromal was predictive of shortened time to categorical disease progression and first respiratory hospitalization but paradoxically was inversely associated with a slower rate of decline in lung function. These findings add to an increasing body of evidence that decline in lung function in IPF is non-linear (Ley 2012, 2015, 2016, Schmidt, Salisbury)

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Table 1

	All subjects n=544
Male / female, n (%)	452 (83) / 92 (17)
Mean age, y (SD)	68.1 (7.3)
Mean BMI	28.4 (4.2)
Current / former / nonsmoker, n (%)	9 (2) / 388 (71) / 147 (27)
North America / Europe / Asia Pacific, n (%)	232 (43) / 214 (39) / 98 (18)
Mean LOXL2 (picogram/ml)	88.2 (61.5)
Mean FVC % predicted (SD)	61.9 (12.2)
Mean FVC L	2.4 (0.6)
Mean FEV ₁ /FVC (SD)	0.82 (0.06)
Mean Hb-corrected DLCO % predicted (SD)	38 (11)
Mean 6MWD, m (SD)	402 (112.9)
Mean SGRQ (SD)	44.6 (18.4)
Mean RV, L (SD)	1.4 (0.4)
Mean HRCT score (SD)*	30.6 (13.1)
Mean IPF Diagnosis Duration, year (SD)	2.0 (2.0)
GAP stage I / II / III, n (%)	96 (18) / 289 (53) / 84 (29)

- For HRCT n=517. While all subjects had subjects had HRCT imaging evaluated at baseline, only 517 had imaging that was amenable to quantification of fibrosis

Table 2

Prediction Span	<i>Selected Predictors</i>	Pearson Correlation	P-value	$\sqrt{\text{(MSE)}}$
52 weeks (Week 14 to Week 66)	• *FVC at 14 week	-0.480	0.001	0.211
	• *RV at baseline		0.002	
	• *FVC change weeks 0-14	0.060	<0.001	
	• SGRQ (change week 0-14)	-2.060		
	• HRCT fibrosis score	-0.002	0.005	
			-0.002	

- *For FVC, change in FVC and RV, the variable is analyzed in 10 ml increments

Table 3

Outcome	Stepwise Selected Baseline Predictors	Hazard Ratio	P-value	C-Index
Time to first Progression Free Survival (PFS) event	• FVC week 14 (required)	0.998	0.043	0.69
	• Change in FVC Week 0-14	0.936	<0.0001	
	• FEV ₁ /FVC	1.034	0.007	
	• HRCT	1.022	<0.0001	
Time to Death	• FVC week14 (required)	0.996	0.323	0.64
	• Change in FVC Week 0-14	0.97	0.017	
	• DLCOPP	0.947	0.006	
	• FEV ₁ /FVC	1.108	0.003	
	• Log (LOXL-2)	2.961	0.013	
	• Log (IPF duration of diagnosis)	0.6333	0.029	

For FVC and change in FVC, the variable is analyzed in 10 ml increments

Table 4

Outcome	Stepwise Selected Baseline Predictors	Hazard Ratio	P-value	C-Index
Time to First Hospitalization	<ul style="list-style-type: none">• FVC (required)• BMI• DLCOPP• FEV₁/FVC• SGRQ• HRCT•	1.001 0.949 0.974 1.034 1.015 1.023	0.491 0.014 0.012 0.034 0.002 0.003	0.76
Time to First Respiratory Hospitalization	<ul style="list-style-type: none">• FVC (required)• Change FVC Week 0-14• DLCOPP• FEV₁/FVC• SGRQ	0.999 0.980 0.948 1.056 1.021	0.773 0.001 <0.0001 0.002 <0.001	0.72

For FVC and change in FVC, the variable is analyzed in 10 ml increments

Table 5

	Δ FVC Week 14-66
*FVC baseline	-0.01 (0.86)
*RV baseline	-0.05 (0.47)
Age	-0.06 (0.43)
BMI	-0.06 (0.19)
DLCOPP baseline	0.09 (0.21)
FEV ₁ /FVC baseline	-0.10 (0.18)
Log(LOXL2) baseline in picogram/ml	0.04 (0.63)
6MWD baseline	0.01 (0.95)
SGRQ baseline	-0.09 (0.22)
HRCT baseline	-0.13 (0.14)
Log(IPF Diagnosis Duration)	0.06 (0.47)

* For FVC and RV, the variable is analyzed in 10 ml increments