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Minimum clinically important difference in Quantitative Lung Fibrosis score associated with all-cause mortality in idiopathic pulmonary fibrosis: subanalysis from two phase II trials of pamrevlumab

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14	5	Grace Hyun J Kim, ¹ Xueping Zhang, ² Matthew S Brown, ¹ Lona Poole, ² Jonathan G Goldin ¹
15 16	c	
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18	7	¹ David Geffen School of Medicine at UCLA Los Angeles CA USA
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20 21	8	² FibroGen, Inc., San Francisco, CA, USA
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24		
25 26	10	Corresponding author:
27	11	Groop Hyper LVim DhD MS
28	11	Grace Hyun J Kim, PhD, MS
29	12	Professor-in-Residence
30 31	16	
32	13	Co-director, Center for Computer Vision and Imaging Biomarkers
33		
34 35	14	Department of Radiological Sciences
36		
37	15	David Geffen School of Medicine at UCLA
38	10	Department of Piestatistics Fielding School of Public at LICLA
39 40	10	Department of Biostatistics Fleiding School of Fublic at OCLA
41	17	924 Westwood Blvd Suite 650
42	1,	
43 11	18	Los Angeles, CA 90024 USA
45		
46	19	E-mail: gracekim@mednet.ucla.edu
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ABSTRACT (300/300 words)

Objectives: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease. Chest high-resolution computed tomography (HRCT) is instrumental in IPF management, and the Quantitative Lung Fibrosis (QLF) score is a computer-assisted metric for quantifying lung disease using HRCT. The aim is to assess the utility of the QLF by estimating a minimum clinically important difference (MCID) that correlates with physiologic lung function and IPF symptoms and also serves as an imaging biomarker to confirm disease progression and response to therapy. **Design and Study setting:** We conducted *post hoc* analyses of prospective data from two Phase II studies of pamrevlumab, a fully human monoclonal antibody that binds to and inhibits connective tissue growth factor activity, slowing lung-function decline in IPF. **Participants:** Overall, 152 patients with follow-up visits after Week 24. Methods: We also conducted a Cox regression analysis to establish a sensitive and robust MCID of the QLF score for the hard outcome of predicting all-cause mortality. We then used the anchor-based Jaeschke's method to estimate the MCID of the QLF score that corresponded with the already established MCID of St. George's Respiratory Questionnaire (SGRQ) and percentpredicted forced vital capacity (ppFVC). **Results:** QLF changes of 1% (HR=4.98, p=0.05), 2% (HR=4.04, p=0.041), 20 mL (HR=6.37, p=0.024), and 22 mL (HR=6.38, p=0.024) predicted mortality. QLF changes of 4.4% and 3.6% corresponded to the established MCID of 5-point increase in SGRQ and a 3.4% reduction in ppFVC, respectively, in the setting of IPF.

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Conclusion: A conservative metric of 2% can be used as the MCID of QLF for predicting all-cause mortality. This may be considered in IPF trials in which the degree of structural fibrosis assessed via HRCT is an endpoint. The MCID of SGRQ and FVC correspond with a greater amount of QLF and may reflect that a greater amount of change in fibrosis is required before there is functional change. Strengths and limitations of this study ▶ This study successfully estimated a minimum clinically important difference (MCID) of quantitative lung fibrosis (QLF) score using HRCT as an imaging biomarker, based on *post hoc* analyses. ► A change in QLF of $\geq 1\%$ or ≥ 20 mL was associated with an increased risk of death in Idiopathic pulmonary fibrosis (IPF), demonstrating the value of early surrogate endpoint of QLF. ▶ The study supports the clinical validity of QLF in IPF as an important marker in IPF with potential implications for disease monitoring and treatment responses. Structural fibrosis assessed via HRCT is a potential efficacy endpoint for IPF, providing an imaging-based measure that may be used in clinical trials and therapeutic evaluations. ► The absence of confirmative positive prospective clinical trial in IPF may limit the ability to fully re-evaluate an MCID of 2% QLF changes as a marker for disease-progression and survival.

70 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive interstitial lung disease that includes symptoms of cough, worsening of dyspnoea, and progressive lung injury and scarring. Together, these symptoms limit physical activity and reduce patient health-related quality of life (HRQOL) [1–3]. There is no cure for IPF [3], and its prognosis is very poor. Median survival is estimated to be no more than 2–5 years after diagnosis [4]. Two approved antifibrotic drugs (pirfenidone and nintedanib) significantly reduce the rate of lung-function decline in IPF [5–7]. However, individual responses to treatment are variable and unpredictable, and HRQOL does not improve [6,7].

Pamrevlumab is a fully human monoclonal antibody that binds to and inhibits the activity of connective tissue growth factor [8-10]. Two phase II studies, one open-label and the other placebo-controlled intravenous administration of pamrevlumab, demonstrated slowing the rate of lung-function decline, progression of lung fibrosis evident on computed tomography (CT), and a trend toward improved HROOL. Adverse events were generally mild [9,10]. However, a recent Phase III trial of pamrevlumab for IPF (ZEPHYRUS-1) did not meet its primary endpoint of absolute change in FVC from baseline to week 48 [11, 12]. Its companion study (ZEPHYRUS-2) was terminated [13].

IPF treatment options are limited, and improved monitoring and a sensitive metric for assessing
therapeutic efficacy are needed. Radiologically detected lung fibrosis correlates with physiologic
lung function and symptomatic changes in IPF, and early and sensitive imaging biomarkers are

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93	needed to confirm disease progression or worsening of forced vital capacity (FVC) and response
94	to therapy as quickly as possible to optimise drug development and patient care [2,3,14–17].
95	
96	FVC is the most common measure for assessing treatment efficacy in IPF [18,19]. HRQOL and
97	other patient-reported outcome (PRO) measures are also important endpoints for evaluating
98	disease progression and treatment efficacy, although they have not been validated in IPF cohorts
99	[3,20]. Use of chest high-resolution CT (HRCT) is expanding and is instrumental in the
100	diagnosis and management of IPF [1]. Computer-assisted methods for quantifying lung disease
101	on HRCT calculate textural features derived from image data and classify different patterns of
102	interstitial lung diseases based on machine learning algorithms [21-23]. Computational
103	quantitative scoring systems that analyse HRCT images have been used as imaging biomarkers
104	in IPF clinical trials to assess the degree and progression of structural lung fibrosis. Of these,
105	Quantitative Lung Fibrosis (QLF) has demonstrated high reproducibility [22–24] (figure 1).
106	QLF is associated with more prospective validation than other quantitative CT techniques and
107	has been used in recent clinical trials of IPF [21,25]. QLF changes of <2% were associated with
108	better long-term survival than changes $\geq 2\%$ for patients with interstitial lung disease in
109	scleroderma [26].
110	
111	The minimum clinically important difference (MCID) is an important standard for determining
112	meaningful changes related to a clinical intervention or measurement tool [27] and represents the
113	smallest detectable and beneficial change [28]. Both distribution-based methods (using variations
114	from repeated measures) and anchor-based approaches (relying on established MCIDs from
115	other relevant clinical variables) are used to determine MCIDs [29]. The MCID of QLF changes

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in an IPF cohort has not been evaluated. For clinically meaningful validation, an MCID of the
QLF threshold should provide a tool for both identifying an effective treatment and detecting a
difference in mortality over time. This is especially important in IPF, which is a progressive
disease with a considerably shorter median survival than other chronic lung diseases [30].

We conducted a *post hoc* analysis of prospective data from two Phase II studies of pamrevlumab.
We estimated the MCID of the QLF score using the anchor-based Jaeschke's method involving
both a PRO measure, St. George's Respiratory Questionnaire (SGRQ), and a functional
parameter, FVC, to assess the QLF change corresponding with these measures of disease. We
conducted a Cox proportional hazards regression analysis to establish the MCID of the QLF for
predicting all-cause mortality.

1 2		
3 4	127	METHODS
5 6	128	
7 8	129	Patients
9 10 11	130	This was a secondary analysis of study 049 [9] and the Phase II PRAISE study [10]. The two
12 13	131	study populations were pooled to include a total of 190 patients with IPF. Eligibility criteria for
14 15	132	the two studies were similar [9,10]. Study 049 (NCT01262001), conducted between March 2011
16 17 19	133	and December 2012 at 18 centres in the United States, was a single-arm, open-label study [9].
18 19 20	134	Pamrevlumab was administered every 3 weeks for 45 weeks: Cohort 1 received 15 mg/kg and
21 22	135	Cohort 2 received 30 mg/kg [9]. PRAISE (Study 067 [NCT01890265]), conducted between
23 24	136	August 2013 and July 2017 at 39 centres throughout North America, Australia, Africa, and
25 26 27	137	Europe, was a double-blind, placebo-controlled study [10]. Patients were randomised to receive
28 29	138	placebo or pamrevlumab 30 mg/kg every 3 weeks for 45 weeks [10].
30 31	139	Local ethics committees / institutional review boards (ECs/IRBs) approved the protocol for each
32 33	140	site, and all patients provided written informed consent before enrollment (Study 049:
34 35 36	141	Aspire IRB00004587; Study 067 (PRAISE): Quorum (now Advarra) 00023875; both studies
37 38	142	WIRB (now WCG IRB) IRB00000533).
39 40	143	
41 42 42	144	Of the 190 patients, 155 had follow-up visits after Week 24 and data from Week-48 visits,
43 44 45	145	including the primary outcome measure of FVC. For both studies, pulmonary function tests,
46 47	146	including spirometry, were performed at baseline and every 12 weeks thereafter, and HRCT was
48 49	147	performed at baseline and every 24 weeks. SGRO was completed at baseline and Weeks 24 and
50 51	148	48 Mortality data were collected for the lengths of the respective studies
52 53 54	149	
55 56	145	Patient and public involvement
57 58		-
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No patients or members of the public were involved in the design, conduct, reporting, ordissemination plans of this study.

QLF scores were estimated from standardised non-contrast thin-section volumetric HRCT scans using an established radiomic texture-based quantification algorithm. QLF uses image normalization (denoising) to minimise cross-site variability within images, resulting in decomposed CT images prior to texture calculation [22]. QLF was measured as extent (%) and volume (mL). **Supplemental figure 1** provides an example of QLF extent (%) and volume (mL) on HRCT and overlaid images for a patient with IPF. QLF measures the amount of reticulation with architectural distortion in the lung. Scores range from 0–100% for extent of fibrosis and from 0 mL to maximum lung volume for volume of fibrosis. Greater scores represent increased fibrosis [10,21]. For this analysis, we considered changes in QLF in the whole lung, which were calculated from the greatest QLF scores at baseline, to be the primary outcome.

166 Estimation of a Minimum Clinically Important Difference

We used the anchor-based Jaeschke's method with predefined criteria for establishing the MCID
of QLF that corresponded with the established MCIDs of SGRQ and percent-predicted FVC
(ppFVC). We used a Cox proportional hazards regression analysis using all-cause mortality as an
anchor by applying several thresholds. Patients did not have follow-up visits if they died or
received a lung transplant.

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The SGRQ is a self-administered questionnaire that assesses HRQOL in respiratory diseases. SGRQ total score ranges from 0–100, and greater scores indicate deteriorating HRQOL. The MCID of the SGRQ was assumed to be ± 5 points [31]. Changes in FVC are often used as primary endpoints in trials of respiratory diseases. The ppFVC is an estimate of lung function, with greater percentages indicating better function. The MCID of ppFVC was assumed to be $\pm 3.4\%$ [32].

Changes in longitudinal QLF scores were initially correlated with established MCID changes in SGRQ and ppFVC. The anchor-based Jaeschke's method was used to estimate the MCID of QLF scores from these changes in SGRQ and ppFVC from baseline at Weeks 24 and 48. Jaeschke's method describes the mean change in the measurement of interest for patients who experience a change in an anchor [30]. Multiple anchors were chosen to obtain robust, unbiased estimates of the MCID [33]. Another anchor-based Cox proportional hazards regression was used for all-cause mortality, in which duration of survival or time to death was used as an anchor. Thresholds tested were derived from a reproducibility study, with incremental increases as extent changes of 1, 2, 3, and 4% and volume changes of 20, 22, 24, and 26 mL [34]. Covariates of age and ppFVC at baseline were adjusted in the regression analysis (Of note that the covariates of sex and ppDLCO were not used in Cox regression due to the imbalanced distribution of sex in the multiple thresholds and the collinearity among ppDLCO, ppFVC, and QLF). Continuous-scale and multiple thresholds of QLF scores were compared to test differences in mortality risk. The clinical repeatability of the QLF score was estimated to be approximately 0.4% ($\approx 2.77 \times 0.14$) in the whole lung using the sum of two variances and 95% statistics [35]. In addition, the MCID from each anchor (SGRQ and ppFVC) was tested in a Cox

1 2		
2 3 4	196	regression model as a threshold. Repeated assessments (or measures) are necessary for
5 6 7	197	estimating reproducibility using a distribution-based method. Because repeated HRCT scans
7 8 9	198	were not available for each patient, an anchor-based approach that relies on the variability of
10 11	199	anchored measurements was selected.
12 13 14	200	
14 15 16	201	Summary statistics are reported for demographics and clinical variables. Continuous variables
17 18	202	are reported as mean and standard deviation (SD), and categorical variables are reported as
19 20 21	203	frequencies and percentages.
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RESULTS

207	
208	There were no notable differences in demographics or baseline characteristics between the
209	cohorts (table 1, supplemental table 1, Supplemental figure 2). The median (IQR) length of
210	the follow-up period was 337 (504) days. Because changes in QLF outcomes for all-cause
211	mortality were derived from Week-24 data and the screening HRCT scan, the median observed
212	survival was relatively short. In total 185 available screening HRCT scans, 33 patients had no
213	available survival analyses after Week 24 because they discontinued prior to Week-24 visits
214	(N=19), or they died prior to Week 24 (N=13) or did not undergo scan (N=1).
215	

Variable	Category	Combined group (Study 049 + Study 067) (N=190)	Study 049 (n=89)	Study 067 (n=101)
Age, y	Mean (SD)	68.1 (7.06)	67.9 (7.04)	68.2 (7.11)
Sex, n (%)	Male	145 (76.3)	71 (79.8)	74 (73.3)
	Female	45 (23.7)	18 (20.2)	27 (26.7)
Race, n (%)	American Indian or			
	Alaska Native	1 (0.5)	1 (1.1)	0
	Asian	8 (4.2)	0	8 (7.9)
	Black or African			
	American	1 (0.5)	1 (1.1)	0
	White	172 (90.5)	87 (97.8)	85 (84.2)
	Other	8 (4.2)	0	8 (7.9)
Weight, kg	n	190	89	101
	Mean (SD)	86.40 (16.46)	89.50 (14.82)	83.67 (17.39)
Time since first	n	189	89	100
IPF diagnosis, y	Mean (SD)	1.60 (1.35)	1.91 (1.54)	1.32 (1.09)

216 Table 1. Demographics and baseline clinical characteristics

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smoking status,	Current	3 (1.6)	0	3 (3.0)
n(0/)	Former	60 (31.6)	0	60 (59 4)
11 (70)	Never	38 (20 0)	0	38 (37.6)
(, ')	Missing	89 (46 8)	89 (100 0)	0
Lung function		09 (10.0)	0) (100.0)	0
FVC L	n	190	89	101
, _	Mean (SD)	2.79 (0.78)	2.73 (0.80)	2.84 (0.76)
FVC. %	n	190	89	101
predicted	Mean (SD)	70.44 (13.42)	66.79 (14.68)	73.66 (11.33)
DLCO, %	n	190	89	101
predicted	Mean (SD)	51.38 (13.72)	48.85 (13.32)	53.61 (13.74)
FEV ₁ /FVC ratio	n	190	89	101
	Mean (SD)	0.81 (0.06)	0.82 (0.06)	0.80 (0.06)
HRCT ^a				
Whole lung	n	185	89	96
volume, L	Mean (SD)	3.95 (1.01)	3.81 (0.94)	4.07 (1.05)
QLF, %	n	185	89	96
	Mean (SD)	16.8 (10.33)	19.6 (11.20)	14.3 (8.76)
QLF, mL	n	185	89	96
	Mean (SD)	622.74 (367.67)	701.13 (395.62)	550.07 (325.1)
GAP ^b				
GAP score	n	190	89	101
	Mean (SD)	3.8 (1.33)	4.1 (1.33)	3.6 (1.30)
Symptom Score			4	
SGRQ	n	186	88	98
	Mean (SD)	44.04 (17.87)	46.24 (14.78)	42.05 (20.11)
UCSD-SOBQ	n	135	89	46
	Mean (SD)	33.10 (20.32)	32 13 (18 68)	21 00 (72 70)

48, QLF ch	anges were 4.3 % nd -2.1 % and -4	% and 108mL and 65mL and –2.8%	d 2.3% and 81n and –54mL, re	nL, respectively, for	or worsene
condition a	nd -2.1% and -6	65mL and –2.8%	and –54mL, re	spectively, for im	1
Tabla 7 D	alatianship of ($\mathbf{V} = \mathbf{E} \left(0 \right)$	and volume (m	L) with the each	proved con
SGRQ and	l FVC using Ja	eschke's method	and volume (m l	il) with the anch	or-dased r
Anchor		A	djusted corres compared wit k 24	sponding QLF va h stable condition Weel	lues n ^a k 48
		•	SGR	Q change	
SGRQ	Whole lung	Decreased	Increased	Decreased ^d	Increas
	QLF, % QLF, mL	$\frac{\leq 0.5\%}{\leq 10 \text{ mL}}$	<u>≥4.4 %</u> ≥91 mL	$\frac{\geq -2.8\%}{\leq -54 \text{ mL}^{\circ}}$	<u>≥2.39</u> ≥81 m
			ppFV	C change	
		Increased ^b	Decreased ^b	Increased ^b	Decreas
ppFVC	QLF, %	\leq -2.0% ^c	≥3.6% ^c	$\leq -2.1\%$	≥4.3%
	QLF, mL	\leq -56 mL ^c	≥65 mL ^c	\leq -65 mL ^c	≥108 n

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Agreement between the two components of symptoms and lung function and their corresponding changes in QLF score are reported in supplemental table 2. Similar percentages of patients experienced concordance in changes at Weeks 24 and 48. If changes in FVC and SGRQ were both considered worsened, the mean (SD) changes in extent of QLF were 8.1% (8.27) at Week 24 and 7.9% (7.37) at Week 48. If changes were both considered stable, the mean (SD) changes in QLF were 0.5% (3.75) at Week 24 and 2.5% (4.31) at Week 48. If changes were both considered improved, the mean (SD) changes in QLF were -1.6% (3.71) at Week 24 and -3.4%(6.50) at Week 48. Overall, the concordant changes for worsening, stability, and improvement followed expected directional changes from negative to positive values in QLF changes. IPF is a complex disease that includes dynamic changes in lung symptoms, function, and structure over time. These changes do not always progress at the same rate, and most patients experienced discordance in symptoms and lung function (supplemental table 2). The discordant changes when one parameter worsened were associated with QLF changes of slightly less than 2% at Week 24 and greater than 2% at Week 48; discordant changes with one parameter improved were associated with OLF changes of approximately 1%. The relationship of OLF changes to each of the MCIDs of SGRQ and ppFVC are provided in supplemental table 3. Unadjusted analyses demonstrated that mean changes in MCIDs were greater compared with the stable group and trended in the correct direction based on the respective anchors. The effect sizes of QLF changes (both extent and volume) were approximately 1 or slightly greater for patient groups with worsened SGRQ scores and worsened ppFVC, indicating a strong relationship

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changes at Week 24, using all-cause mortality, Cox proportional hazards model revealed a four-

to nine-fold increased risk of death for patients with sizeable changes in QLF at Week 24

(table 4). This indicates QLF as a sensitive marker for changes relative to SGRQ and ppFVC.

)

Table 3. Cox proportional hazards model using all-cause mortality as an anchor with QLF

287 with cutoff of Week 24 changes

QLF changes in whole lung	Total patients (N=152)	Total deaths (n=11) (%)	HR (95% CI)	P -Value
Continuous, %			1.20 (1.08, 1.34)	0.001
Continuous, mL			1.01 (1.01, 1.02)	0.000
Week 24 QLF changes in whole lung	Total patients meeting listed threshold,	Total deaths meeting listed threshold,	HR (95% CI)	P -Value

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	n (%)	n (%)		
≥0%	118 (78)	9 (82)	1.48 (0.31, 7.02)	0.623
≥0 mL	99 (65)	9 (82)	2.57 (0.55, 12.1)	0.232
Thresholds				
<u>QLF %</u> ≥1%	101 (66)	9 (82)	4.98 (1.00, 24.8)	0.050
≥2%	87 (57)	8 (73)	4.04 (1.06, 15.4)	0.041
≥3%	66 (43)	6 (55)	4.69 (1.24, 17.7)	0.023
≥4%	50 (33)	5 (45)	4.52 (1.18, 17.3)	0.028
QLF volume				
≥20 mL	84 (55)	8 (73)	6.37 (1.27, 32.0)	0.024
≥22 mL	83 (55)	8 (73)	6.38 (1.27, 32.0)	0.024
≥24 mL	81 (53)	8 (73)	6.83 (1.37, 34.2)	0.019
>26 mL	80 (53)	8 (73)	7.63 (1.51, 38.6)	0.014
Note: mean chang	ge from previously n	nodelled measure	ement variation of QLF o	f 0.4% (2.77 ×
Note: mean chang 2×SD). CI, confidence int deviation. Table 4. Anchor - ppFVC and SGF	ge from previously n terval; HR, hazard ra -based Cox proport RQ as anchors	nodelled measurd atio; QLF, quanti tional hazards n	ement variation of QLF or tative lung fibrosis; SD, s nodel with an MCID der	f 0.4% (2.77 × standard
Note: mean chang 2×SD). CI, confidence inf deviation. Table 4. Anchor - ppFVC and SGR	ge from previously n terval; HR, hazard ra -based Cox proport RQ as anchors Tota	nodelled measure atio; QLF, quanti tional hazards n	ement variation of QLF of tative lung fibrosis; SD, s nodel with an MCID der al Risk of deat	f 0.4% (2.77 × standard rived from h,
Note: mean chang 2×SD). CI, confidence int deviation. Table 4. Anchor - ppFVC and SGF	ge from previously n terval; HR, hazard ra -based Cox proport RQ as anchors Tota (N=15	nodelled measure atio; QLF, quanti tional hazards n d Tot 55) Deaths	ement variation of QLF of tative lung fibrosis; SD, s nodel with an MCID den al Risk of death (n=11) HR (95% C	rived from h, <i>P</i> -Valu
Note: mean chang 2×SD). CI, confidence int deviation. Table 4. Anchor- ppFVC and SGF	ge from previously n terval; HR, hazard ra -based Cox proport RQ as anchors Tota (N=15 n whole lung by ppl	nodelled measure atio; QLF, quanti tional hazards n al Tot 55) Deaths (FVC with ±3.4%	ement variation of QLF of tative lung fibrosis; SD, s nodel with an MCID der al Risk of death (n=11) HR (95% Cl	f 0.4% (2.77 × standard rived from h, <i>P</i> -Valu I)
Note: mean chang 2×SD). CI, confidence int deviation. Table 4. Anchor- ppFVC and SGF QLF changes in ≥3.6%	ge from previously n terval; HR, hazard ra -based Cox proport RQ as anchors Tota (N=15 n whole lung by ppl 41 (27	nodelled measure atio; QLF, quanti tional hazards n al Tot 55) Deaths FVC with ±3.4% %) 4 (36	ement variation of QLF of tative lung fibrosis; SD, s nodel with an MCID der al Risk of death (n=11) HR (95% C 5 as anchor %) 4.33 (1.14, 16	tived from h, P-Valu () () () () () () () () () ()

≥4.4%	
	.17 (1.63, 23.4) 0.007
≥91 mL	.35 (1.98, 27.3) 0.003
CI, confidence inte ppFVC, percent-pro George's Respirato results from table 2	Illy important difference; lung fibrosis; SGRQ, St. es, marked with bold fonts,

300 DISCUSSION

This study established the MCID for change in QLF score in the setting of IPF as it relates to all-cause mortality. A minimum threshold of change in QLF of 1% or 20 mL at Week 24 was associated with an increased risk of death for patients with IPF. To include changes observed with SGRQ and FVC, a conservative estimate of 2% can be adopted as the MCID of QLF, based on the Week-24 mean QLF changes when patients experienced worsening of either ppFVC or SGRQ. An increased risk of death was also associated with sizeable QLF changes using Jaeschke's method with anchors of IPF symptoms (SGRQ) and lung function (ppFVC) to determine MCID.

Changes in QLF were consistent with changes in SGRQ and ppFVC, and mean QLF changes coincided with both symptom and lung-function changes. Changes in QLF and SGRQ were positively correlated, and changes in QLF and ppFVC were inversely correlated. This indicates that, generally, a responder in IPF clinical trial was associated with a reduction in QLF, a reduction in SGRQ, and an incremental increase in ppFVC. The mean MCID of QLF for improved symptoms was close to zero at Week 24 compared with the reduction in MCID for improved lung function, but reduced in both symptomatic changes and functional changes at Week 48 (see **table 2** for the details). In contrast, the MCID of QLF for worsened symptoms had a greater magnitude at Week 24 than the MCID for worsened lung function, but at Week 48, functional changes were greater than symptomatic changes (see **table 2** for the details). This suggests that symptomatic changes (measured by SGRQ) improve slower or more inconsistently than functional changes (FVC) for improvement but were sensitive in worsening faster. This is

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likely a result, in part, of the effects of limited symptom recall and the subjective nature ofHRQOL.

325

Quantitative HRCT tools for measuring pulmonary fibrosis is a critical in a therapeutic 326 development in ILD to confirm efficacy or evaluate safety of an experimental drug. Assessments 327 328 of QLF change have mostly served as secondary or exploratory quantitative imaging outcomes to estimate changes in lung fibrosis in clinical trials. QLF score based on HRCT images is traceable 329 and can visualise regions of fibrosis. The incremental changes in QLF extent (%) or volume 330 (mL) highlight the structural worsening in IPF that is associated with decreased FVC. The 331 incremental worsening in ppFVC confirms that FVC is a reasonably reliable assessment in IPF 332 and supports its use as the primary efficacy endpoint in clinical trials. A role of quantitative tools 333 in future can be expanded in patient care using digital AI platform, when a trial is approved with 334 a positive outcome from a primary endpoint or a secondary endpoint of an imaging outcome. 335 336

In this *post hoc* analysis of prospective clinical trial data, a sensitivity-based method was used to 337 establish the MCID of QLF and an anchor-based method was used to estimate the MCID of QLF 338 339 associated with established MCIDs of SGRQ and ppFVC. Sensitivity-based methods for estimating MCID ideally require a baseline variable or characteristic to reliably quantify disease 340 341 severity. For HRCT-based QLF, this requires repeat HRCT scans in a coffee break-type (i.e., 342 approximately 15 minutes) [36,37] of experiment for patients with IPF, but this method poses ethical challenges because of the unnecessary risk of radiation exposure. The variability can be 343 344 estimated statistically [25], but we recognise this as a limitation of the analysis. Anchor-based 345 methods require measurements of longitudinal change for the tool of interest and other anchor

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measurements that already have an established MCID. The estimates of MCIDs from other
anchored measurements are likely overestimated because of the nature of additive variabilities.
MCID estimates are approximations, and the recommended approach is to use multiple anchors
to define a range of MCID estimates [38]. Both function and PROs are relevant when
interpreting the outcomes of clinical trials.

The MCIDs of the relationships between OLF and FVC (function) or SGRO (PRO) in this study were less sensitive than the MCID of QLF using all-cause mortality as an anchor. The degree of QLF change needed to attain a meaningful, absolute change was 2.0–4.3% for FVC as an anchor, 2.3–4.4% for SGRQ as an anchor, and -1.6%–8.1% for concordance of FVC and SGRQ in non-stable change. This suggests that, for a meaningful change in function and PROs derived from Jaeschke's method, a greater amount of QLF change is needed in the evaluation of QLF with FVC or SGRQ than when using all-cause mortality as an anchor with multiple QLF thresholds. This reflects the progressive nature of IPF, which contrasts other chronic lung diseases, and the fact that the observations from the follow-up visits are based on stable or worsening disease. This is similar to findings by Kon et al., who reported that the MCID of an assessment tool for chronic obstructive pulmonary disease from a receiver operating characteristic (ROC) analysis was smaller than the MCID from an anchor-based approach [39]. Further, multivariate regression modelling, such as the anchor-based Jaeschke's method, that combine both clinical and subjective (e.g., PRO) parameters to quantify changes in the outcome of interest (e.g., QLF) offer less-biased estimates of MCIDs than distribution-based methods, which only assess the statistical significance of a change [40].

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The QLF changes of 1% and 2% at Week 24 presented in **supplemental figures 3a** and **3b**, respectively, correspond to 25- and 46-mL changes. The structural changes are visualised both in the right side (supplemental figure 3a) and left side of the lung (supplemental figure 3b). These QLF changes are similar to the absolute mean changes of 2% and 56 mL (table 2) when FVC was used as an anchor in our analysis. When retesting the MCID of the QLF score derived from the MCID using SGRQ and ppFVC as anchors, the hazard ratio (HR) ranged from 4.33– 8.89, which is similar to the HRs of 4.98 and 4.04 for the relatively smaller MCIDs of 1% and 2%, respectively. The QLF scores associated with the MCIDs of SGRQ and ppFVC were greater than the QLF score associated with survival, which suggests that these biomarkers require greater structural disease progression before they can detect meaningful change. This also suggests that QLF may be more sensitive than either ppFVC or SGRQ as a trial endpoint [41]. There were 11 deaths in this study that occurred after Week 24. Because QLF changes were derived from Week 24 and the screening HRCT scans, the median survivals were relatively short. Week-48 data were omitted from the survival analysis because most changes in QLF were observed within 24 weeks. In addition, including data beyond Week 24 had the potential to skew the results by including patients with mild to moderate IPF who were more likely to remain alive at 1 year. QLF change as a volume is a suitable clinical trial endpoint, as noted by the high HR in table 4. Change in QLF extent can provide a normalised measurement regardless of the volume differences between patients of different sex or height. Finally, the MCID of QLF is an early biomarker of change in lung fibrosis, so 48 weeks of data, which is often used for the primary endpoints in IPF clinical trials, are not needed to determine the value of the MCID of the QLF score and its clinical applicability for predicting early change.

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393	The multiple thresholds of QLF changes can be found in other studies. In an independent cohort
394	of patients who received nintedanib (n=42) anti-fibrotic approved drug, mean absolute changes
395	in QLF were 0.98% and a 21.7-mL increase at Month 6, and 1.4% and a 27.6-mL increase at
396	Month 12. In the placebo arm of the same trial, the changes were 1.33% and 37.3mL at Month 6
397	and 2.2% and 67.0mL at Month 12. Negative correlations were observed between change in QLF
398	score and change in FVC at Month 6, supporting the findings of the QLF score [21]. In a
399	retrospective analysis of approximately 200 patients with IPF, 4% change in QLF score for the
400	most severe lobe and for the whole lung at 6 months was associated with a three- to five-fold
401	increased risk of clinical progression [42]. Further, a placebo-controlled Phase II trial of 137
402	patients with IPF reported significant correlations between QLF and ppFVC changes, as well as
403	other symptoms of IPF, where the most of subjects in the placebo arm were within $\pm 2\%$ changes
404	at week 24 [25]. Overall, QLF measured on HRCT, where the most of 6 month mean changes
405	range from 1-4%, has proven to be useful as an efficacy endpoint in clinical trial settings.
406	
407	This study has several limitations. First, it was a <i>post hoc</i> rather than an <i>a priori</i> analysis of data
408	from two Phase II clinical trials. Thus, due to the nature of Phase II studies, mortality was based
409	on a short follow-up period. In addition, allocation of treatment arms and study locations were
410	different between the studies. Specifically, Study 049 was a single-arm study, whereas Study 067

411 was a randomised study with one-to-one allocation of placebo and pamrevlumab. Further, Study

412 049 took place only in the United States, and Study 067 involved patients worldwide. Sub-

413 cohorts of patients who received pamrevlumab or other treatments were not analysed separately

414 here for purposes of simplification. Additionally, this study analysed the usefulness of QLF

change for predicting mortality risk only over a short period of time. Second, we did not estimate MCID using a distribution-based approach because the extra radiation exposure required for patients to estimate the MCID was not well-justified. Third, a single quantitative HRCT score for IPF was applied. The estimated MCID may not be generalizable to other available quantitative scores. Fourth, caution should be applied when applying the estimated MCID for the observational or registry studies, in which HRCT scans are not performed routinely. In this study, HRCT scans were scheduled and performed as part of clinical trials. Lastly, phase III studies did not show efficacy of pamrevlumab [11-13], this study used survival as the primary endpoint to assess MCID. We believe our analyses begin the evidence-generation process of using multiple thresholds for validation of a biomarker [43]. The MCID of QLF in IPF has demonstrated clinical validity. The estimated MCID of 2% may be considered for associating changes in mortality, lung function, and patient symptoms in ongoing and future trials of IPF, where the metric can be normalised to the volume of QLF changes for both sexes. The greater MCID of QLF using the MCID of SGRQ and ppFVC may suggest that structural changes precede functional changes. The change of QLF volume is a sensitive measurement that can be considered in applying an imaging outcome as a potential efficacy endpoint when the extent of structural fibrosis is assessed via HRCT.

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459	Patient and public involvement No patients or members of the public were involved in the
460	design, conduct, reporting, or dissemination plans of this study.
461	Patient consent for publication Consent obtained directly from patient(s).
462	Provenance and peer review Not commissioned; externally peer reviewed.
463	Data availability statement FibroGen, Inc., is committed to data sharing and to furthering
464	medical research and patient care. Based on scientific merit, requests from qualified external
465	researchers for anonymised patient-level and study-level clinical trial data (including redacted
466	clinical study reports) for medicines and indications approved in the United States and Europe
467	will be considered after the respective primary study is accepted for publication. All data
468	provided are anonymised to respect the privacy of patients who have participated in the trial in
469	line with applicable laws and regulations.
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480	Grace Hyun J Kim https://orcid.org/0000-0003-1225-3489

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Supplemental table 1. I	Demographics and base	eline clinical charac	teristics using med	ian and range

Variahle	Category	Combined group (Study 049 +	Study 049	Study 067
v al labit	Category	Study 047 (N=190)	(n=89)	(n=101)
Age, y	Median (range)	68 (46-82)	68 (47-82)	68 (46-80)
Weight, kg	()		89.1 (56.8–	()
8,0	Median (range)	86.3 (46–127.6)	121.8)	82.7 (46–127.6)
Time since first		- Co		
IPF diagnosis, y	Median (range)	1.1 (0–6.0)	1.5 (0.1–6.0)	0.9 (0.0-4.9)
Lung function				
FVC, L	Median (range)	2.62 (1.28-5.51)	2.53 (1.32-5.51)	2.78 (1.28-4.45
FVC, %	Median (range)	69.5 (42.6–	65.9 (42.6–	71.8 (53.9–
predicted		111.7)	111.7)	102.1)
DLCO, %	Median (range)	49.8 (28.2–94.5)	47.4 (30.4–94.5)	53.6 (28.2-85.9
predicted				
FEV ₁ /FVC ratio	Median (range)	0.82 (0.65-0.95)	0.83 (0.65-0.94)	0.81 (0.66-0.95
HRCT ^a				
Whole lung	Median (range)	3.91 (1.52-6.49)	3.57 (2.40-6.49)	4.09 (1.52-6.33
volume, L				
QLF, %	Median (range)	15 (2–52)	18 (2–51)	13 (2–52)
QLF, mL	Median (range)	559.65 (66.02-	619.31 (66.02–	494.94 (86.18-
		2325.50)	2325.50)	1603.94)
GAP ^b				
GAP score	Median (range)	4 (0–7)	4 (1–7)	4 (0-6)
Symptom Score				

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1 2 2					open-202	
3 4	SGRQ	Median (range)	42.5 (0.8-86.4)	45.6 (11.3–81.4)		
5	UCSD-SOBQ	Median (range)	30.0 (1.0-85.0)	30.0 (2.1-85.0)	31.0 (1.0-83.0)	
6 7 8	DLCO, diffusing gender, age, phys fibrosis; SD, stan	capacity for carbon biology; HRCT, high dard deviation; SGR	monoxide; FEV ₁ , fe -resolution compute .Q, St. George's Re	orced expiratory volu ed tomography; IPF, spiratory Questionna	idiopathic pulmonary fibroses; QLF, quantitative lung ire; UCSD-SOBQ, Universet, QLF, and California San Diego,	
9 10	Shortness of Brea	ath Questionnaire.			inse inse	
11	^a Computer-assiste	ed QLF scores were	derived from volun	netric scans of the wh	nole lung.	
12	^b Gender-Age-Pul	lmonary (GAP) func	tion score.		ited n 55.	
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	Cha	anges in QLF score (mean (SD)	%),
	Week	24	
	SGRQ improved	SGRQ stable	SGRQ worsened
	(≤−5),	(-5 to 5),	(≥5),
	n=48	n=63	n=41
ppFVC improved	n=5	n=11	n=4
(≥3.4%), n=20			
	-1.6 (3.71)	-1.3 (3.98)	0.5 (0.58)
ppFVC stable	n=31	n=36	n=17
(-3.4% to 3.4%), n=84			
	0.9 (2.94)	0.5 (3.75)	2.1 (3.04)
ppFVC worsened	n=12	n=16	n=20
(≤-3.4%), n=48			
	2.3 (2.42)	1.7 (3.32)	8.1 (8.27)
	Week	48	
	SGRQ improved	SGRQ stable	SGRQ worsened
	(≤−5),	(-5 to 5),	(≥5),
	n=40	n=54	n=39
ppFVC improved	n=5	n=11	n=3
(≥3.4%), n=19			
	-3.4 (6.50)	0.6 (2.11)	0.7 (1.53)
ppFVC stable	n=24	n=23	n=15
(-3.4% to 3.4%), n=62			
	0.3 (3.65)	2.5 (4.31)	1.9 (4.09)
ppFVC worsened	n=11	n=20	n=21
(≤– 3.4%), n= 5 2			
	19(327)	5.5 (5.90)	7.9 (7.37)

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 BMJ Open ppFVC, percent-predicted forced vital capacity; QLF, quantitative lung fibrosis; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

ed discordanc, 0.5%+17×2.1%+12×, x>5.5%)(3+15+11+20) = 3., y+12×2.3%)((11+4+31+12) = 0.7%, 0)/(11+3+24+11) = 0.8%. Note: mean QLF changes when patients experienced *discordance of symptoms* were calculated as follow EF worsening of one parameter, mean QLF change at Week $24 = (4 \times 0.5\% + 17 \times 2.1\% + 12 \times 2.3\% + 16 \times 1.7\%)/(4 + 17 + 12 + 16) = 1\frac{9}{2}\%$ gmean QLF change at Week $48 = (3 \times 0.7\% + 15 \times 1.9\% + 11 \times 1.9\% + 20 \times 5.5\%)/(3 + 15 + 11 + 20) = 3.3\%$. For improvement of one parameter, mean QLF change at Week $24 = (11 \times -1.3\% + 4 \times 0.5\% + 31 \times 0.9\% + 12 \times 2.3\%)/(11 + 4 + 31 + 12) = 0.7\%\%$; mean QLF change at W is 38 = 12%y 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de seignement Superieur (ABES) . s related to text and data mining, Al training, and similar technologies. $(11 \times 0.6\% + 3 \times 0.7\% + 24 \times 0.3\% + 11 \times 1.9\%)/(11 + 3 + 24 + 11) = 0.8\%.$

							Week 24				u d) on		
				SGR	2						ppFV	12 Ma En		
		Unadju analy	isted sis	Adjusted analysis, mean (95% CI)	Unadju analy	sted sis	Adjusted analysis, mean (95% CI)		Unadju analy	isted rsis	Adjusted analysis, mean (95% CI)	seignement Sul related to text	sted sis	Adjusted analysis mean (95% CI)
	N	QLF change, % mean (95% CD	ES	QLF change, % mean (95% CD	QLF change, mL mean (95% CD	ES	QLF change, mL mean (95% CD	N	QLF change, % mean (95% CD	ES	QLF change, % mean (95% CD	and day and	ELF ES Effange, SomL Benean Southerstein Sou	QLF change, mL mean (95% CD
Combined g	roup		1			1	6							
Worsened ^a	41	4.88 (3.46, 6.30)	1.08	4.39 (2.97, 5.81)	111.94 (77.60, 146.28)	1.03	90.81 (56.47, 125.15)	20	-1.00 (-3.01, 1.01)	0.23	-1.99 (-4.00, 9	1 8.46 (<u>-</u> 67.92,	0.17	-55.69 (-105.15 6.24)
Stable ^a	63	0.49 (-0.66, 1.64)	0.11	0 (-1.15, 1.15)	21.13 (-6.58, 48.83)	0.19	$\begin{array}{r} 0\\ (-27.71,\\ 27.70) \end{array}$	86	0.99 (0.02, 1.96)	0.22	0.02 0 (-0.97, 0.97)	1 7.23 1 7.23 1 3.38, 1 08)	0.33	0.00 (-23.85, 23.85)
Improved ^a	48	1.00 (-0.32, 2.32)	0.22	$\begin{array}{c} 0.51 \\ (-0.81, \\ 1.83) \end{array}$	31.27 (-0.47, 63.01)	0.29	$ \begin{array}{r} 10.14 \\ (-21.60, \\ 41.88) \end{array} $	49	4.55 (3.27, 5.83)	1.02	3.56 (2.28, 4.84)	E)1.90 (%0.30, (%3.49)	0.93	64.67 (33.07, 96.26)
Study 049			1			I				I		dies t		
Worsened ^a	22	6.59 (4.16, 9.02)	1.21	6.38 (3.95, 8.81)	137.19 (82.92, 191.45)	1.12	124.14 (69.87, 178.40)	8	-2.63 (-6.56, 1.31)	0.56	-3.90 (-7.83, 0.04)	A (- 198.12, b) (8)	_ 0.56	-97.22 (-185.82 8.62)
Stable ^a	29	0.21	0.04	0	13.05	0.11	0	44	1.27	0.23	0	91 7.70	0.30	0.00

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		(-1.91,		(-2.12,	(-34.22,		(-47.27,		(-0.41,		(-1.68,	₩ . (₽ 0.08,		(-37.78,
		2.32)		2.11)	60.31)		47.26)		2.95)		1.68)	8 .48)		37.78)
Improved ^a	22	1.27	0.23	1.06	30.96	0.25	-17.91	22	6.50	1.21	5.23	5 9.62	1.08	91.92
		(-1.15,		(-1.36,	(-23.30,		(-36.65,		(4.12,		(2.85, 4	(ě 6.20,		(38.50,
		3.70)		3.49)	85.23)		72.18)		8.88)		7.61)	<u>a</u> 1 <u>8</u> 3.05)		145.35)
Study 067												! Maj Ens		
Worsened ^a	19	2.89	0.98	2.15	82.71	0.93	54.69	12	0.08	0.03	-0.61	e 6 8.91	0.10	-27.84
		(1.47,		(0.73,	(39.77,		(11.75,		(-1.68,		(-2.37,	2 2 6 .70		(-83.44,
		4.32)		3.58)	125.65)		97.63)		1.84)		1.15)			27.78)
Stable ^a	34	0.74	0.24	0	28.02	0.30	0	42	0.69	0.23	0.00	3 6.74	0.39	0.00
		(-0.33,		(-1.07,	(-4.08,		(-32.10,		(-0.25,		(-0.94,	ອັ ດ 7.01,		(-29.73,
		1.80)		1.06)	60.12)		32.10)		1.63)		0.94)	e . 6 6.46)		29.73)
Improved ^a	26	0.77	0.25	0.03	31.53	0.35	3.51	27	2.96	1.00	2.27	g ⊑ <u>∓</u> 9.30	0.85	42.56
		(-0.45,		(-1.19,	(-5.18,		(-33.2,		(1.79,		(1.10,	$\mathbf{D}_{2.23}$		(5.49,
		1.99)		1.25)	68.24)		40.22)		4.14)		3.45)	6.38		79.76)
							Week 48				9	'bmj		
				SGR	Q						FVC	open.		
		Unadju	isted	Adjusted	Unadju	isted	Adjusted	<u> </u>	Unadju	isted	Adjusted	nadju	sted	Adjusted
		analy	sis	analysis,	analy	sis	analysis,		analy	sis	analysis,	analys	sis	analysis,
				mean			mean				mean	or		mean
				(95%) CD			(95%) CD				(95%) CD			(95%) CD
	NT		EC			EC		NI		FC		<u>† 5</u> 9 1 1 1	FC	
		QLF	ES	QLF	QLF	ES	QLF	IN	QLF	ES	QLF		ES	QLF
					mI		change,					o cheange,		mI
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		(95%		(95%)	(95%)		(95%)		(95%		(95%)			(95%)
		()370 CD												()370 CD
Combined g	group	CI		CI										CIJ
Worsened ^a	42	5 52	1 01	2 30	157 32	1 17	80.75	20	-0.65	_	-2.13	- ö i 6 46		-64 84
										0.14		gra	0.13	
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		(3.82, 7.23)		(0.60, 4.01)	(115.54, 199.10)		(38.97, 122.53)		(-2.90, 1.60)		(-4.38, 0.12)	-202475.81, (-1-092.90)		(-124.19, -5.48)
Stable ^a	54	3.22 (1.72, 4.73)	0.58	0 (-1.50, 1.51)	76.57 (39.72, 113.42)	0.57	$ \begin{array}{c} 0 \\ (-36.85, \\ 36.85) \end{array} $	62	1.48 (0.20, 2.76)	0.29	0.00 (-1.28, 0 1.28)	uding (0,4.67, 60,4.67, 10, 82,09)	0.36	$\begin{array}{c} 0.00 \\ (-33.71, \\ 33.71) \end{array}$
Improved ^a	41	$\begin{array}{c} 0.39\\ (-1.34,\\ 2.12) \end{array}$	0.07	-2.83 (-4.56, -1.10)	$\begin{array}{c} 22.14 \\ (-20.15, \\ 64.42) \end{array}$	0.17	-54.53 (-96.72, -12.15)	53	5.75 (4.37, 7.14)	1.14	4.27 (2.89, 5.66)	Uses religion 202, 45)	1.18	$ \begin{array}{r} 107.61 \\ (71.14, \\ 144.07) \end{array} $
Study 049)			••••=)	1	12.10)		()	1	0.00)	ated	1	1
Worsened ^a	23	5.83 (3.06, 8.59)	0.91	1.02 (-1.75, 3.78)	167.85 (97.11, 238.60)	1.03	57.98 (-12.76, 128.73)	11	-1.73 (-5.05, 1.60)	0.35	-2.46 (-5.78, 0.87)	ownloaded to text and d to text and d to text and d to text and d to text and d	0.36	-62.90 (-157.66, 31.86)
Stable ^a	26	4.81 (2.21, 7.41)	0.75	0 (-2.60, 2.60)	109.87 (43.33, 176.41)	0.67	0 (-66.54, 66.54)	22	0.73 (-1.62, 3.08)	0.14	0.00 (-2.35, 2.35)	A A B C C C C C C C C C C	0.08	0.00 (-67.01, 67.00)
Improved ^a	17	-0.59 (-3.80, 2.62)	0.09	-5.40 (-8.61, -2.19)	-20.49 (- 102.78, 61.80)	0.13	-130.36 (-212.65, -48.07)	33	6.70 (4.78, 8.62)	1.24	5.97 (4.05, 7.89)	d. Al trainin	1.18	169.32 (114.61, 224.03)
Study 067		I					1		1,	1	Ģ	m j.co	I	I
Worsened ^a	19	5.16 (3.18, 7.14)	1.26	3.41 (1.43, 5.39)	144.57 (102.25, 186.90)	1.65	98.92 (56.6, 141.25)	9	0.67 (-2.38, 3.71)	0.17	-1.23 (-4.28, 1.81)	similar (42.90, (43.01)	0.28	-43.07 (-111.03, 24.88)
Stable ^a	28	1.75 (0.12, 3.38)	0.42	0 (-1.63, 1.63)	45.65 (10.78, 80.51)	0.51	0 (-34.87, 34.86)	40	1.90 (0.46, 3.34)	0.42	0.00 (-1.44, 1.44)	Chinolog 1920.36)	0.68	$ \begin{array}{c} 0.00 \\ (-32.23, \\ 32.23) \end{array} $
Improved ^a	24	$ \begin{array}{r} 1.08 \\ (-0.68, \\ 2.85) \end{array} $	0.26	-0.67 (-2.43, 1.10)	52.33 (14.67, 89.99)	0.59	6.68 (-30.98, 44.34)	20	4.20 (2.16, 6.24)	0.96	2.30 (0.26, 4.34)	a 3.39 (a 7.81, 108.97)	1.16	45.26 (-0.32, 90.84)

 Note: Negative sign denotes decline in ppr v C. CI, confidence interval; ES, effect size; FVC, forced vital capacity; MCID, minimum clinically important ungere predicted forced vital capacity; QLF, quantitative lung fibrosis; SGRQ, St. George's Respiratory Questionna Note: Negative sign denotes decline in ppFVC.

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1 2 3 4 5 6 7 8 9	^a Worsened: SGRQ change \geq 5 points or ppFVC change \leq -3.4%; stable: SGRQ change between -5 and 5 between -3.4% and 3.4%; improved: SGRQ change \leq -5 points or ppFVC change \geq 3.4%.	njopen-2024559 on 12 May r copyright francluding for uses
11 12 13 14 15 16 17 18 19 20 21		2025. Downloaded from http://b ignement Superieur (ABES) . elated to text and data mining,
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Minimum clinically important difference in Quantitative Lung Fibrosis score associated with all-cause mortality in idiopathic pulmonary fibrosis: subanalysis from two phase II trials of pamrevlumab

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18	7	¹ David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;
19 20		
21	8	² FibroGen, Inc., San Francisco, CA, USA
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25	10	Corresponding author:
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27 20	11	Grace Hyun J Kim, PhD, MS
20 29		
30	12	Professor-in-Residence
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32 33	13	Co-director, Center for Computer Vision and Imaging Biomarkers
34	14	Department of Radiological Sciences
35	1.	
36 37	15	David Geffen School of Medicine at UCLA
38		
39	16	Department of Biostatistics Fielding School of Public at UCLA
40 41	47	024 Westerned Dired Switz (50
42	17	924 Westwood Blvd, Suite 630
43	18	Los Angeles CA 90024 USA
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46	19	E-mail: gracekim@mednet.ucla.edu
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ABSTRACT (300/300 words)

Objectives: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease. Chest high-resolution computed tomography (HRCT) is instrumental in IPF management, and the Quantitative Lung Fibrosis (QLF) score is a computer-assisted metric for quantifying lung disease using HRCT. The aim is to assess the change in QLF score associated with a minimum clinically important difference (MCID) of IPF symptoms and physiologic lung function, and also determine the MCID of QLF change associated with all-cause mortality to serve as an imaging biomarker to confirm disease progression and response to therapy. **Design and Study setting:** We conducted *post hoc* analyses of prospective data from two IPF Phase II studies of pamrevlumab, a fully human monoclonal antibody that binds to and inhibits connective tissue growth factor activity. **Participants:** Overall, 152 patients with follow-up visits after Week 24. Methods: We used the anchor-based Jaeschke's method to estimate the MCID of the QLF score that corresponded with the already established MCID of St. George's Respiratory Questionnaire (SGRQ) and percent-predicted forced vital capacity (ppFVC). We also conducted a Cox regression analysis to establish a sensitive and robust MCID of the QLF score in predicting all-cause mortality. **Results:** QLF changes of 4.4% and 3.6% corresponded to the established MCID of 5-point increase in SGRQ and a 3.4% reduction in ppFVC, respectively. QLF changes of 1%(HR=4.98, *p*=0.05), 2%(HR=4.04, *p*=0.041), 20 mL(HR=6.37, *p*=0.024), and 22 mL(HR=6.38, *p*=0.024) predicted mortality.

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Conclusion: A conservative metric of 2% can be used as the MCID of QLF for predicting all-cause mortality. This may be considered in IPF trials in which the degree of structural fibrosis assessed via HRCT is an endpoint. The MCID of SGRQ and FVC correspond with a greater amount of QLF and may reflect that a greater amount of change in fibrosis is required before there is functional change. Strengths and limitations of this study ▶ This study successfully estimated a minimum clinically important difference (MCID) of quantitative lung fibrosis (QLF) score using HRCT as an imaging biomarker, based on post hoc analyses. ▶ A 24-Week change in QLF from baseline of $\geq 1\%$ or ≥ 20 mL was associated with an increased risk of death in Idiopathic pulmonary fibrosis (IPF), demonstrating its value as an early predictive endpoint. ▶ The study supports the clinical validity of QLF as an important marker in IPF with potential implications for disease monitoring and treatment responses. Structural fibrosis assessed via HRCT is a potential efficacy endpoint for IPF, providing an imaging-based measure that may be used in clinical trials and therapeutic evaluations. ▶ The absence of confirmative positive prospective clinical trial in IPF may limit the ability to fully re-evaluate an MCID of 2% QLF changes as a marker for disease-progression and survival.

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71 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive interstitial lung disease that includes symptoms of cough, worsening of dyspnoea, and progressive lung injury and scarring. Together, these symptoms limit physical activity and reduce patient health-related quality of life (HRQOL) [1–3]. There is no cure for IPF [3], and its prognosis is very poor. Median survival is estimated to be no more than 2–5 years after diagnosis [4]. Two approved antifibrotic drugs (pirfenidone and nintedanib) significantly reduce the rate of lung-function decline in IPF [5–7]. However, individual responses to treatment are variable and unpredictable, and HRQOL does not improve [6,7]. Identifying individual small, detectable, and clinically meaningful changes of patient-level correlation will be beneficial for both physicians and patients in making informed decisions for available antifibrotic treatments and for on-going novel therapeutic discovery in clinical trials. Pamrevlumab is a fully human monoclonal antibody that binds to and inhibits the activity of connective tissue growth factor [8-10]. Two phase II studies, one open-label and the other placebo-controlled intravenous administration of pamrevlumab, demonstrated slowing the rate of lung-function decline, progression of lung fibrosis evident on computed tomography (CT), and a trend toward improved HRQOL. Adverse events were generally mild [9,10]. However, a recent Phase III trial of pamrevlumab for IPF (ZEPHYRUS-1) did not meet its primary endpoint of absolute change in forced vital capacity (FVC) from baseline to week 48 [11, 12]. Its companion

IPF treatment options are limited, and improved monitoring and a sensitive metric for assessing
therapeutic efficacy are needed. Radiologically detected lung fibrosis correlates with physiologic

study (ZEPHYRUS-2) was terminated [13].

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lung function and symptomatic changes in IPF, and early and sensitive imaging biomarkers are 95 needed to confirm disease progression or worsening of FVC and response to therapy as quickly 96 as possible to optimise drug development and patient care [2,3,14–17]. 97

FVC is the most common measure for assessing treatment efficacy in IPF [18,19]. HROOL and 99 100 other patient-reported outcome (PRO) measures are also important endpoints for evaluating disease progression and treatment efficacy including St. George's Respiratory Questionnaire 101 (SGRQ) [3,20]. Use of chest high-resolution CT (HRCT) is expanding and is instrumental in the 102 103 diagnosis and management of IPF [1]. Computer-assisted methods for quantifying lung disease on HRCT calculate textural features derived from image data and classify different patterns of 104 interstitial lung diseases based on machine learning algorithms [21–23]. Computational 105 106 quantitative scoring systems that analyse HRCT images have been used as imaging biomarkers in IPF clinical trials to assess the degree and progression of structural lung fibrosis. Of these, 107 Quantitative Lung Fibrosis (QLF) has demonstrated high reproducibility [22–24] (figure 1). 108 QLF is associated with more prospective validation than other quantitative CT techniques and 109 has been used in recent clinical trials of IPF [21,25]. In two phase 2 IPF trials of pamrevlumab, 110 significant correlations were observed between QLF changes and the changes in percent-111 predicted FVC (ppFVC) (ranging from -0.51 to -0.64), as well as with changes in PRO, SGRQ 112 (ranging from 0.27 to 0.30) [9, 10, 26]. Furthermore, QLF changes of <2% were associated with 113 114 better long-term survival than changes $\geq 2\%$ for patients with interstitial lung disease in 115 scleroderma [27]. 116

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The minimum clinically important difference (MCID) is an important standard for determining meaningful changes related to a clinical intervention or measurement tool [28] and represents the smallest detectable and beneficial change [29]. Both distribution-based methods (using variations from repeated measures) and anchor-based approaches (relying on established MCIDs from other relevant clinical variables) are used to determine MCIDs [30]. The MCID of QLF changes in an IPF cohort has not been evaluated. For clinically meaningful validation, an MCID of the QLF threshold should provide a tool for both identifying an effective treatment and detecting a difference in mortality over time. This is especially important in IPF, which is a progressive disease with a considerably shorter median survival than other chronic lung diseases [31]. Our aim is to assess the change in QLF score associated with MCID of a PRO measure, SGRQ, and a key measure in lung function physiology, FVC, using the anchor-based Jaeschke's method, and to determine the MCID of QLF change based on its association with all-cause mortality through a *post hoc* analysis of prospective data from two Phase II studies of pamrevlumab, exploring the potential of QLF as an imaging marker to confirm disease progression and response to therapy.

1 2		
3 4	133	METHODS
5 6	134	
7 8	135	Patients
9 10 11	136	This was a secondary analysis of study 049 [9] and the Phase II PRAISE study [10]. The two
12 13	137	study populations were pooled to include a total of 190 patients with IPF. Eligibility criteria for
14 15	138	the two studies were similar [9,10]. Study 049 (NCT01262001), conducted between March 2011
16 17 18	139	and December 2012 at 18 centres in the United States, was a single-arm, open-label study [9].
19 20	140	Pamrevlumab was administered every 3 weeks for 45 weeks: Cohort 1 received 15 mg/kg and
21 22	141	Cohort 2 received 30 mg/kg [9]. PRAISE (Study 067 [NCT01890265]), conducted between
23 24	142	August 2013 and July 2017 at 39 centres throughout North America, Australia, Africa, and
25 26 27	143	Europe, was a double-blind, placebo-controlled study [10]. Patients were randomised to receive
28 29	144	placebo or pamrevlumab 30 mg/kg every 3 weeks for 45 weeks [10].
30 31	145	Local ethics committees / institutional review boards (ECs/IRBs) approved the protocol for each
32 33 24	146	site, and all patients provided written informed consent before enrollment (Study 049:
35 36	147	Aspire IRB00004587; Study 067 (PRAISE): Quorum (now Advarra) 00023875; both studies
37 38	148	WIRB (now WCG IRB) IRB00000533).
39 40	149	
41 42 43	150	Of the 190 patients, 155 had follow-up visits after Week 24 and data from Week-48 visits,
44 45	151	including the primary outcome measure of FVC. For both studies, pulmonary function tests,
46 47	152	including spirometry, were performed at baseline and every 12 weeks thereafter, and HRCT was
48 49	153	performed at baseline and every 24 weeks. SGRQ was completed at baseline and Weeks 24 and
50 51 52	154	48. Mortality data were collected for the lengths of the respective studies.
53 54	155	
55 56	156	Patient and public involvement
57 58		8
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No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Outcomes

QLF scores were estimated from standardised non-contrast thin-section volumetric HRCT scans using an established radiomic texture-based quantification algorithm. QLF uses image normalization (denoising) to minimise cross-site variability within images prior to texture calculation [22]. QLF was measured as extent (%) and volume (mL). Supplemental figure 1 provides an example of QLF extent (%) and volume (mL) on HRCT and overlaid images for a patient with IPF. QLF measures the amount of reticulation with architectural distortion in the lung. Scores range from 0–100% for extent of fibrosis and from 0 mL to total lung capacity for volume of fibrosis. Greater scores represent increased fibrosis [10,21]. For this analysis, we considered 24-Week or 48-Week changes in QLF in the whole lung, which were calculated from the QLF scores of baseline HRCT.

Estimation of a Minimum Clinically Important Difference

We used the anchor-based Jaeschke's method with predefined criteria for establishing the MCID of QLF that corresponded with the established MCIDs of SGRQ and ppFVC. We used a landmark Cox proportional hazards regression analysis using all-cause mortality as an anchor by applying several thresholds of 24-Week QLF changes. Patients did not have follow-up visits if they died or received a lung transplant.

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179	The SGRQ is a self-administered questionnaire that assesses HRQOL in respiratory diseases.
180	SGRQ total score ranges from 0-100, and greater scores indicating deterioration in HRQOL
181	and in this study SGRQ was used to represent severity of symptoms. The MCID of the SGRQ
182	was assumed to be ± 5 points [32]. Changes in FVC are often used as primary endpoints in trials
183	of respiratory diseases. The ppFVC is an estimate of lung function, with greater percentages
184	indicating better function. The MCID of ppFVC was assumed to be $\pm 3.4\%$ [33]. In this study,
185	SGRQ was used to represent severity of symptoms, and lung function, respectively.
186	
187	Changes in longitudinal QLF scores were initially correlated with established MCID changes in
188	SGRQ and ppFVC. The anchor-based Jaeschke's method was used to estimate the MCID of
189	QLF scores from these changes in SGRQ and ppFVC from baseline at Weeks 24 and 48.
190	Jaeschke's method describes the mean change in the measurement of interest for patients who
191	experience a change in an anchor [31]. Multiple anchors were chosen to obtain robust, unbiased
192	estimates of the MCID [34]. Another anchor-based Cox proportional hazards regression was
193	used for all-cause mortality, in which duration of survival or time to death was used as an
194	anchor. A preliminary threshold was derived from a previous reproducibility study [35] and six-
195	month change observed in a clinical trial [21]. The reproducibility coefficient of QLF score was
196	estimated to be approximately 0.4% ($\approx 2.77 \times 0.14 = \sqrt{2} \times 1.96 \times 0.14$) [35, 36] and the mean of
197	six-month change was 0.98% for extent QLF and 21.7 mL for volume QLF from a nintedanib
198	arm [21] Thresholds increased incrementally as extent changes of 1, 2, 3, and 4% and volume
199	changes of 20, 22, 24, and 26 mL [21, 35]. Covariates of age and ppFVC at baseline were
200	adjusted in the regression analysis (Of note that the covariates of sex and percent-predicted
201	diffusing Capacity of Lungs for Carbon Monoxide (ppDLCO) were not used in Cox regression

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202	due to the imbalanced distribution of sex in the multiple thresholds and the collinearity among
203	ppDLCO, ppFVC, and QLF). Continuous-scale and multiple thresholds of QLF scores were
204	compared to test differences in mortality risk. In addition, the MCID from each anchor (SGRQ
205	and ppFVC) was tested in a Cox regression model as a threshold.
206	
207	Summary statistics are reported for demographics and clinical variables. Continuous variables
208	are reported as mean and standard deviation (SD), and categorical variables are reported as
209	frequencies and percentages.
210	
211	

RESULTS

213	
214	There were no notable differences in demographics or baseline characteristics between the
215	cohorts (table 1, supplemental table 1). The median (±Inter Quartile Range) length of the
216	follow-up period was 337 (±504) days. Because changes in QLF outcomes for all-cause
217	mortality were derived from Week-24 data and the screening HRCT scan, the median observed
218	survival was relatively short. In total 185 available screening HRCT scans, 33 patients had no
219	available survival analyses after Week 24 because they discontinued prior to Week-24 visits
220	(N=19), or they died prior to Week 24 (N=13) or did not undergo scan (N=1) (Supplemental
221	figure 2).
222	
223	Table 1. Demographics and baseline clinical characteristics
	Combined

225 I abit 1. Demographics and Dasenne ennear enaracteristics

Variable	Category	Combined group (Study 049 + Study 067) (N=190)	Study 049 (n=89)	Study 067 (n=101)
Age, y	Mean (SD)	68.1 (7.06)	67.9 (7.04)	68.2 (7.11)
Sex, n (%)	Male	145 (76.3)	71 (79.8)	74 (73.3)
	Female	45 (23.7)	18 (20.2)	27 (26.7)
Race, n (%)	American Indian or Alaska Native	1 (0 5)	1(11)	0
	Asian	8 (4.2)	0	8 (7.9)
	Black or African			
	American	1 (0.5)	1 (1.1)	0
	White	172 (90.5)	87 (97.8)	85 (84.2)
	Other	8 (4.2)	0	8 (7.9)
Weight, kg	n	190	89	101
	Mean (SD)	86.40 (16.46)	89.50 (14.82)	83.67 (17.39)

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IPF diagnosis, y Tobacco smoking status, n (%) Lung function	Mean (SD) Current Former Never	$ \begin{array}{r} 1.60 (1.35) \\ 3 (1.6) \\ \hline 60 (21.6) \end{array} $	1.91 (1.54)	1 32 (1 09)
Tobacco smoking status, n (%) Lung function	Current Former Never	3 (1.6)		1.52 (1.07)
smoking status, r. (%) Lung function	Former Never	60 (21 6)	0	3 (3.0)
(%) Lung function	Never	00 (31.0)	0	60 (59.4)
Lung function		38 (20.0)	0	38 (37.6)
Lung function	Missing	89 (46.8)	89 (100.0)	0
			· · ·	
FVC, L	n	190	89	101
	Mean (SD)	2.79 (0.78)	2.73 (0.80)	2.84 (0.76)
FVC, %	n	190	89	101
predicted	Mean (SD)	70.44 (13.42)	66.79 (14.68)	73.66 (11.3
DLCO, %	n	190	89	101
predicted	Mean (SD)	51.38 (13.72)	48.85 (13.32)	53.61 (13.74
FEV ₁ /FVC ratio	n	190	89	101
	Mean (SD)	0.81 (0.06)	0.82 (0.06)	0.80 (0.06)
HRCT ^a	C C			
Whole lung	n	185	89	96
volume, L	Mean (SD)	3.95 (1.01)	3.81 (0.94)	4.07 (1.05)
QLF, %	n	185	89	96
	Mean (SD)	16.8 (10.33)	19.6 (11.20)	14.3 (8.76)
QLF, mL	n	185	89	96
	Mean (SD)	622.74 (367.67)	701.13 (395.62)	550.07 (325.
GAP ^b				
GAP score	n	190	89	101
	Mean (SD)	3.8 (1.33)	4.1 (1.33)	3.6 (1.30)
Symptom Score				
SGRQ	<u>n</u>	186	88	98
	Mean (SD)	44.04 (17.87)	46.24 (14.78)	42.05 (20.1
UCSD-SOBQ	n	135	89	46
	Mean (SD)	33.10 (20.32)	32.13 (18.68)	34.98 (23.2
UCSD-SOBQ DLCO, diffusing o	n Mean (SD) capacity for carbon capacity: GAP get	$\frac{135}{33.10 (20.32)}$ monoxide; FEV ₁ , for nder, age, physiology;	89 32.13 (18.68) ced expiratory volu HRCT, high-resolu ntitative lung fibros	46 34.98 (2 me in 1 seco ition compu is; SD, stan

233	Anchor-based analyses assessed the relationship between QLF and the established MCIDs for
234	SGRQ, ppFVC (table 2), or both (supplemental table 2). Thresholds of QLF changes (extent
235	and volume) at Week 24 were 4.4% and 91 mL for symptomatic worsening, respectively, when
236	applying Jaeschke's method using SGRQ as an anchor, and 3.6% and 65 mL for worsening lung
237	function, respectively, when using ppFVC as an anchor. For improved condition of symptom by
238	SGRQ or lung function by ppFVC, the thresholds of QLF changes were $\leq 0.5\%$ and 10mL, and –
239	2.0% and -56mL, respectively. At Week 48 for worsened condition, the thresholds of QLF
240	changes were 2.3% and 81mL by SGRQ, and 4.3% and 108mL by ppFVC, respectively, and for
241	improved condition the QLF changes were –2.8% and –54mL by SGRQ, and –2.1% and –65mL
242	by ppFVC, respectively.

Table 2. Relationship of QLF extent (%) and volume (mL) with the anchor-based MCID of

SGRQ and FVC using Jaeschke's method

Anchor	Adjusted corresponding QLF values of thresholds compared with stable condition ^a						
		Weel	x 24	Week 48			
			SGR	Q change			
				0.			
SGRQ	Whole lung	Improved ^b	Worsened	Improved ^b	Worsened ^b		
		(N=48)	b	(N=41)	(N=42)		
			(N=41)				
	QLF, %	≤0.5%	≥4.4 %°	$\leq -2.8\%^{c}$	≥2.3%		
	95% CI	[-1.5, 2.5]	[2.3, 6.5]	[-5.4, -0.2]	[-0.3, 4.9]		
	QLF, mL	≤10 mL	≥91 mL ^c	\leq -54 mL	≥81 mL ^c		
	95% CI	[-38, 58]	[41, 141]	[-118, 9]	[18, 144]		
			ppFV	C change			
		Improved ^b	Worsened	Improved ^b	Worsened ^b		
		(N=20)	b	(N=20)	(N=53)		
		(1(20)	(N=49)	(1 (20)	(1, 55)		

ppFVC	QLF, %	$\leq -2.0\%$	≥3.6% ^c	$\leq -2.1\%$	≥4.3% ^c
	95% CI	[-4.5, 0.6]	[1.7, 5.4]	[-5.1, 0.8]	[2.1, 6.4]
	QLF, mL	\leq -56 mL	≥65 mL ^c	\leq -65 mL	≥108 mL ^c
	95% CI	[-118, 7]	[20, 110]	[-143, 13]	[51, 164]
CI, confide difference; SGRQ, St. ^a Shifted by figures. ^b Worsened -5 and 5 po points or p ^c Two 95%	ence interval; FV ppFVC, percent George's Respire the mean change SGRQ change oints or ppFVC pFVC change \geq CIs of the differ	⁷ C, forced vital ca t-predicted forced ratory Questionna ges at ±5 points S ³ ≥5 points or ppF change between – 3.4%. rence between the	apacity; MCID, l vital capacity; hire. GRQ and $\pm 3.4\%$ VC change $\leq -3.4\%$ and 3.4% improved and	Minimum clinica QLF, quantitative % ppFVC; stated v 3.4%; stable: SGF 5; improved: SGR stable groups and	Ily important e lung fibrosis; with 2 significant RQ change betwee Q change ≤ -5 the difference
between w ANOVA n statement.	orse and stable g nodel in the mod	groups are not over lel. Comparisons	erwrapped. 95% are obtained fro	6 CIs were obtained on the same mode	ed from an one-w el using LSMEAN
Agreement	t between the two	o components of	symptoms and	lung function and	their correspond
experienced concordance in changes at Weeks 24 and 48. If changes in SGRQ and FVC were					
both considered worsened, the mean (SD) changes in extent of QLF were 8.1% (8.27) at Week					
24 and 7.9% (7.37) at Week 48. If changes were both considered stable, the mean (SD) changes					
in QLF we	re 0.5% (3.75) a	t Week 24 and 2.	5% (4.31) at W	eek 48. If change	s were both
considered $((.50) \text{ at } \mathbf{V})$	improved, the n	nean (SD) change	es in QLF were	-1.6% (3.71) at V	Week 24 and -3.4
followed ex	xpected direction	nal changes in QI	LF scores.	sennig, stability, i	and improvement
IPF is a con	mplex disease th	at includes dynar	nic changes in	lung symptoms, f	unction, and
structure or	ver time. These	changes do not al	ways progress	at the same rate, a	nd most patients
experience	d discordance in	symptoms and lu	ung function. T	he discordant cha	nges when one
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parameter worsened were associated with the mean QLF changes of approximately 2%; discordant changes with one parameter improved were associated with QLF changes of approximately within $\pm 1\%$, (supplemental table 2). The relationship of QLF changes to each of the MCIDs of SGRQ and ppFVC are provided in supplemental table 3. Unadjusted analyses demonstrated that mean changes in MCIDs were greater (e.g. 4.88%, 95% CI (3.46, 6.30) vs. 4.39% 95% CI (2.97, 5.81) when applying SGRQ as an anchor at Week 24) compared with the stable group (e.g. 0.49%, 95% CI (-0.31, 2.32) vs. 0.00%, 95% CI (-1.15, 1.15) when applying SGRQ as an anchor) and trended in the correct direction. The effect sizes of QLF changes (both extent and volume) were approximately 1 or slightly greater for patient groups with worsened SGRQ scores and worsened ppFVC (i.e. 1.08 for extent and 1.03 for volume when applying SGRQ as an anchor, 1.02 for extent, and 0.93 for volume when applying ppFVC as an anchor, respectively), indicating a strong relationship between QLF and the anchor parameter. The effect sizes for worsened conditions were greater than those observed for patients with not-worsened conditions (i.e. 0.93, 0.33, -0.17 for worsening, stable, and better in the effect size of QLF volume change, respectively, when applying ppFVC as an anchor).

A Cox proportional hazards regression model of QLF changes is presented in **table 3**. Changes ranging from 1–4% and from 20–26 mL were associated with statistically significant differences in all-cause mortality. A minimum threshold of a 1% change in QLF at Week 24 was associated with an increased risk of death. A two- to five-fold increased risk of death was observed for patients with sizeable changes in QLF (i.e., changes greater than the thresholds established by the single-variable anchor-based analyses). Supplemental figures 3a and 3b present patients

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295	with IPF with QLF changes of 1% (25 mL) and 2% (46 mL), respectively, at Week 24. We used
296	an MCID derived from the increase in SGRQ and the decrease in ppFVC, which indicates of
297	worsening in IPF, from table 2. After applying these thresholds, estimated MCID from QLF
298	changes at Week 24, using all-cause mortality, Cox proportional hazards model revealed a four-
299	to nine-fold increased risk of death for patients with sizeable changes in QLF at Week 24
300	(table 4). Significant differences were observed from 1% to 4% changes (20-26mL for QLF
301	volume) (table 3), whereas 4.4% or 3.6% changes (or 91mL or 65mL) for volume changes)
302	were derived from the changes of QLF corresponding to the anchors of SGRQ and ppFVC,
303	respectively (table 4).
304	

Table 3. Cox proportional hazards model using all-cause mortality as an anchor with QLF

with cutoff of Week 24 changes

QLF changes in whole lung	Total patients (N=152)	Total deaths (n=11) (%)	HR (95% CI)	<i>P</i> -Value			
Continuous ⁺ , %			1.20 (1.08, 1.34)	0.001			
Continuous ⁺ , mL			1.01 (1.01, 1.02)	0.000			
Week 24	Total patients	Total					
QLF changes in whole lung	meeting listed threshold, n (%)	deaths meeting listed threshold, n (%)	HR (95% CI)	P -Value			
≥0%	118 (78)	9 (82)	1.48 (0.31, 7.02)	0.623			
≥0 mL	99 (65)	9 (82)	2.57 (0.55, 12.1)	0.232			
Thresholds							
QLF %							
≥1%	101 (66)	9 (82)	4.98 (1.00, 24.8)	0.050			
≥2%	87 (57)	8 (73)	4.04 (1.06, 15.4)	0.041			

	≥3%	66 (43)	6 (55)	4.69 (1.24, 17.7)	0.023			
	<u>≥4%</u>	50 (33)	5 (45)	4.52 (1.18, 17.3)	0.028			
	QLF volume							
	≥20 mL	84 (55)	8 (73)	6.37 (1.27, 32.0)	0.024			
	≥22 mL	83 (55)	8 (73)	6.38 (1.27, 32.0)	0.024			
	≥24 mL	81 (53)	8 (73)	6.83 (1.37, 34.2)	0.019			
	≥26 mL	80 (53)	8 (73)	7.63 (1.51, 38.6)	0.014			
	 the proportional h CI, confidence inter deviation. 	azards assumption be rval; HR, hazard rati	o; QLF, quantita	d met using Schoenfield resid ative lung fibrosis; SD, stand	duals. dard			
	Table 4. Anchor-b	ased Cox proportio	onal hazards mo	odel with an MCID derive	d from			
	SGRQ and ppFVC as anchors							
		Total	Tota	Risk of death,	D Val			
		(N=155)) Deaths (n	n=11) HR (95% CI)	P-val			
	QLF changes in v	vhole lung by SGR	Q using ±5 as a	nchor				
	QLF changes in v ≥4.4%	vhole lung by SGR 27 (18%	Q using ± 5 as at (36%)	nchor 6.17 (1.63, 23.4)	0.007			
	QLF changes in v ≥4.4% ≥91 mL	vhole lung by SGR 27 (18% 47 (31%	Q using ± 5 as at b) 4 (36%) b) 6 (55%)	nchor 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3)	0.007			
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w	vhole lung by SGR 27 (18% 47 (31% hole lung by ppFV	Q using ± 5 as a (-) 4 (36%) (-) 6 (55%) C with $\pm 3.4\%$ a	nchor %) 6.17 (1.63, 23.4) %) 7.35 (1.98, 27.3) s anchor	0.00			
_	QLF changes in v ≥4.4% ≥91 mL QLF changes in w ≥3.6%	vhole lung by SGR 27 (18% 47 (31% hole lung by ppFV 41 (27%	Q using ± 5 as a (a) 4 (36%) (b) 6 (55%) C with $\pm 3.4\%$ a (c) 4 (36%)	nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor 6) 4.33 (1.14, 16.5)	0.007			
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w ≥3.6% ≥65 mL	vhole lung by SGR 27 (18% 47 (31% hole lung by ppFV 41 (27% 60 (39%	Q using ± 5 as at a) 4 (36%) b) 6 (55%) C with $\pm 3.4\%$ a b) 4 (36%) c) 7 (64%)	nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor 6) 4.33 (1.14, 16.5) 6) 8.89 (2.13, 37.0)	0.00			
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w ≥3.6% ≥65 mL CI, confidence interppFVC, percent-prederers George's Respirator results from table 2	vhole lung by SGR 27 (18% 47 (31% hole lung by ppFV 41 (27% 60 (39% cval; HR, hazard rati edicted forced vital c ry Questionnaire. (N	Q using ± 5 as at (a) 4 (36%) (b) 6 (55%) C with $\pm 3.4\%$ a (c) 4 (36%) (c) 7 (64%) (c) MCID, minimized (c) MCID, minimized	achor b 6.17 (1.63, 23.4) b 7.35 (1.98, 27.3) s anchor b 4.33 (1.14, 16.5) b 8.89 (2.13, 37.0) num clinically important diffuantitative lung fibrosis; SC based values, marked with leased values.	0.00 0.00 0.00 0.03 0.00 ference; GRQ, St. bold fonts			

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DISCUSSION

> This study established the MCID for change in QLF score in the setting of IPF as it relates to all-cause mortality. A minimum threshold of change in QLF of 1% or 20 mL at Week 24 was associated with an increased risk of death for patients with IPF. To include changes observed with SGRQ and FVC, a conservative estimate of 2% can be adopted as the MCID of QLF, based on the Week-24 mean QLF changes when patients experienced worsening of either SGRQ or ppFVC. An increased risk of death was also associated with sizeable QLF changes using Jaeschke's method with anchors of IPF symptoms (SGRQ) and lung function (ppFVC) to determine MCID.

Changes in QLF were consistent with changes in SGRQ and ppFVC, and mean QLF changes coincided with both symptom and lung-function changes. Changes in QLF and SGRQ were positively correlated, and changes in QLF and ppFVC were inversely correlated [9, 10, 26]. This indicates that, generally, a responder in IPF clinical trial was associated with a reduction in QLF, a reduction in SGRO, and an increase in ppFVC. The threshold of QLF change for improved symptoms was close to zero (i.e. 0.5%) at Week 24 compared with the reduction (-2.0%) in MCID for improved lung function, but at Week 48, further reduced in both symptomatic changes (i.e. -2.8%) and functional changes (-2.1%) (see table 2 for the details). In contrast, the threshold of QLF change for worsened symptoms had a greater magnitude at Week 24 (i.e. 4.4%) than the threshold for worsened lung function (i.e. 3.6%), but at Week 48, functional changes (i.e. 4.3%) were greater than symptomatic changes (i.e. 2.3%) (see table 2 for the details). This suggests that symptomatic changes (measured by SGRQ) improve slower or more inconsistently than

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36 37 38	359
39 40	360
41 42	261
43 44	201
45 46	302
47 48 49	363
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functional changes (FVC) for improvement but were sensitive in worsening faster. This is likely 344 a result, in part, of the effects of limited symptom recall and the subjective nature of HRQOL. 345 346 Quantitative HRCT tools for measuring pulmonary fibrosis is a critical in a therapeutic 347 development in ILD to confirm efficacy or evaluate safety of an experimental drug [18, 21, 25]. 348 349 Assessments of QLF change have mostly served as secondary or exploratory quantitative imaging outcomes to estimate changes in lung fibrosis in clinical trials [11, 13, 25]. QLF score 350 based on HRCT images is traceable and can visualise regions of fibrosis. The incremental 351 changes in QLF extent (%) or volume (mL) highlight the structural worsening in IPF that is 352 associated with decreased FVC [10]. The incremental worsening in ppFVC from Week 24 and 353 Week 48 confirms that FVC is a reasonably reliable assessment in IPF and supports its use as the 354 primary efficacy endpoint in clinical trials [19]. A role of quantitative tools in future can be 355 expanded in patient care using digital AI platform, when a trial is approved with a positive 356 outcome from a primary endpoint or a secondary endpoint of an imaging outcome. 357 358 In this post hoc analysis of prospective IPF clinical trial data, an anchor-based method was used 359 360 to estimate the threshold of QLF change associated with established MCIDs of SGRQ and ppFVC, and a sensitivity-based method was used to establish the MCID of QLF from all-cause 361 362 mortality. Sensitivity-based methods for estimating MCID ideally require a baseline variable or 363 characteristic to reliably quantify disease severity. For HRCT-based QLF, this requires repeat HRCT scans in a coffee break-type (i.e., approximately 15 minutes) [37,38] of experiment for 364 365 patients with IPF, but this method poses ethical challenges because of the unnecessary risk of

radiation exposure. The variability can be estimated statistically [25], but we recognise this as a

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limitation of the analysis. Because repeated HRCT scans were not usually available, an anchor-based approach, that relies on the variability of anchored measurements, was selected in this study. Anchor-based methods require measurements of longitudinal change for the tool of interest and other anchor measurements that already have an established MCID. The estimates of MCIDs from other anchored measurements are likely overestimated because of the nature of additive variabilities. MCID estimates are approximations, and the recommended approach is to use multiple anchors to define a range of MCID estimates [37]. Both function and PROs are relevant when interpreting the outcomes of clinical trials. The MCIDs of the relationships between QLF and SGRQ (PRO) or FVC (lung function) in this study were less sensitive than the MCID of QLF using all-cause mortality as an anchor. The degree of QLF change needed to attain a meaningful, absolute change was 0.5-4.4% for SGRQ as an anchor, 2.0-4.3% for FVC as an anchor, and -1.6%-8.1% for concordance of SGRQ and FVC in non-stable change. This suggests that, for a meaningful change in PROs and function derived from Jaeschke's method, a greater amount of QLF change is needed in the evaluation of QLF with SGRQ or FVC than when using all-cause mortality as an anchor with multiple QLF thresholds. This reflects the progressive nature of IPF, which contrasts other chronic lung diseases, and the fact that the observations from the follow-up visits are based on stable or worsening disease. This is similar to findings by Kon et al., who reported that the MCID of an assessment tool for chronic obstructive pulmonary disease from a receiver operating characteristic (ROC) analysis was smaller than the MCID from an anchor-based approach [40]. Further, multivariable regression modelling, such as the anchor-based Jaeschke's method, that combine both clinical and subjective (e.g., PRO) parameters to quantify changes in the outcome
390	of interest (e.g., QLF) offer less-biased estimates of MCIDs than distribution-based methods,
391	which only assess the statistical significance of a change [41].
392	
393	The QLF changes of 1% and 2% at Week 24 presented in supplemental figures 3a and 3b ,
394	respectively, correspond to 25- and 46-mL changes. The structural changes are visualised both in
395	the right side (supplemental figure 3a) and left side of the lung (supplemental figure 3b).
396	These QLF changes are similar to the absolute mean changes of 2% and 56 mL (table 2) when
397	FVC was used as an anchor in our analysis. When retesting the MCID of the QLF score derived
398	from the MCID using SGRQ and ppFVC as anchors, the hazard ratio (HR) ranged from 4.33-
399	8.89, which is similar to the HRs of 4.98 and 4.04 for the relatively smaller MCIDs of 1% and
400	2%, respectively. The QLF scores associated with the MCIDs of SGRQ and ppFVC were greater
401	than the QLF score associated with survival, which suggests that these biomarkers require
402	greater structural disease progression before they can detect meaningful change. This also
403	suggests that QLF may be more sensitive than either ppFVC or SGRQ as a trial endpoint [42].
404	
405	There were 11 deaths in this study that occurred after Week 24. Because QLF changes were
406	derived from Week 24 and the screening HRCT scans, the median survivals were relatively
407	short. Week-48 data were omitted from the survival analysis because most changes in QLF were
408	observed within 24 weeks. In addition, including data beyond Week 24 had the potential to skew
409	the results by including patients with mild to moderate IPF who were more likely to remain alive
410	at 1 year. QLF change as a volume is a suitable clinical trial endpoint, as noted by the high HR in
411	table 4. Change in QLF extent can provide a normalised measurement regardless of the volume
412	differences between patients of different sex or height. Finally, the MCID of QLF is an early

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biomarker of change in lung fibrosis, so 48 weeks of data, which is often used for the primary endpoints in IPF clinical trials, are not needed to determine the value of the MCID of the OLF score and its clinical applicability for predicting early change.

> The multiple thresholds of QLF changes can be found in other studies. In an independent cohort of patients who received nintedanib (n=42) anti-fibrotic approved drug, mean absolute changes in QLF were 0.98% and a 21.7-mL increase at Month 6, and 1.4% and a 27.6-mL increase at Month 12. In the placebo arm of the same trial, the changes were 1.33% and 37.3mL at Month 6 and 2.2% and 67.0mL at Month 12. Negative correlations were observed between change in QLF score and change in FVC at Month 6, supporting the findings of the QLF score [21]. In a retrospective analysis of approximately 200 patients with IPF, 4% change in QLF score for the most severe lobe and for the whole lung at 6 months was associated with a three- to five-fold increased risk of clinical progression [43]. Further, a placebo-controlled Phase II trial of 137 patients with IPF reported significant correlations between OLF and ppFVC changes, as well as other symptoms of IPF, where the most of subjects in the placebo arm were within $\pm 2\%$ changes at week 24 [25]. Overall, QLF measured on HRCT, where the most of 6 month mean changes range from 1-4%, has proven to be useful as an efficacy endpoint in clinical trial settings.

This study has several limitations. First, it was a *post hoc* rather than an *a priori* analysis of data from two Phase II clinical trials. Thus, due to the nature of Phase II studies, mortality was based on a short follow-up period. In addition, allocation of treatment arms and study locations were different between the studies. Specifically, Study 049 was a single-arm study, whereas Study 067 was a randomised study with one-to-one allocation of placebo and pamrevlumab. Further, Study

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049 took place only in the United States, and Study 067 involved patients worldwide. Sub-cohorts of patients who received pamrevlumab or other treatments were not analysed separately here for purposes of simplification. Additionally, this study analysed the usefulness of QLF change for predicting mortality risk only over a short period of time. Second, we used MCID derived from a distribution-based approach for ppFVC and the symmetric changes in ± 5 points SGRQ, which is close to 4.9 changes reported by Prior et al for deterioration, where most IPF subjects feel worsening or stable in their symptoms. We used ± 5 where the subject-level changes of SGRQ is an integer change, and MCID of SGRQ considered to be around 4-5 points [32, 45, 46]. Third, we did not estimate MCID using a distribution-based approach because the extra radiation exposure required for patients to estimate the MCID was not well-justified. Fourth, a single quantitative HRCT score for IPF was applied. The estimated MCID may not be generalizable to other available quantitative scores. Fifth, caution should be applied when applying the estimated MCID for the observational or registry studies, in which HRCT scans are not performed routinely. In this study, HRCT scans were scheduled and performed as part of clinical trials. Lastly, phase III studies did not show efficacy of pamrevlumab [11-13], this study used survival as the primary endpoint to assess MCID.

We believe our analyses begin the evidence-generation process of using multiple thresholds for validation of a biomarker [44]. The MCID of QLF in IPF has demonstrated clinical validity. The estimated MCID of 2% may be considered for associating changes in mortality, lung function, and patient symptoms in ongoing and future trials of IPF, where the metric can be normalised to the volume of QLF changes for both sexes. The greater MCID of QLF using the MCID of SGRQ and ppFVC may suggest that structural changes precede functional changes. The change of QLF Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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volume is a sensitive measurement that can be considered in applying an imaging outcome as a In extent of s. potential efficacy endpoint when the extent of structural fibrosis is assessed via HRCT.

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51 52	485	an employee of and holds stock options in Pliant Therapeutics, Inc. XZ was an employee of
53 54 55	486	FibroGen, Inc., at the time of the study, but is now an employee of and holds stock options in
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Neumora Therapeutics, Inc. JGG and MSB are former founders of MedOIA and board members of Voiant. GJK is a former consultant to MedQIA and current consultant to Voiant. GJK, MSB, and JGG are a patent developer of the issued patent: UC-2013-078-2-LA-EP. **Patient and public involvement** No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this study. **Patient consent for publication** Consent obtained directly from patient(s). Provenance and peer review Not commissioned; externally peer reviewed. Data availability statement FibroGen, Inc., is committed to data sharing and to furthering medical research and patient care. Based on scientific merit, requests from qualified external researchers for anonymised patient-level and study-level clinical trial data (including redacted clinical study reports) for medicines and indications approved in the United States and Europe will be considered after the respective primary study is accepted for publication. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. **Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise. **Open access**

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2 3	510	ORCID iD	
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FIGURE LEGENDFigure 1. Use of HRCT to calculate QLF. QLF is a specific method (UCLA patent) that utilises

672 image normalization (denoising) to minimise cross-site variability within images, resulting in

673 decomposed CT images prior to texture calculation.

675 Footnote: CT, computed tomography; HRCT, high-resolution computed tomography; LF, lung

676 fibrosis; QLF, quantitative lung fibrosis; UCLA, University of California at Los Angeles

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Figure 1. Use of HRCT to calculate QLF. QLF is a specific method (UCLA patent) that utilises image normalization (denoising) to minimise cross-site variability within images, resulting in decomposed CT images prior to texture calculation. /CT, computed tomography; HRCT, high-resolution computed tomography; LF, lung fibrosis; QLF, quantitative lung fibrosis; UCLA, University of California at Los Angeles.

417x157mm (38 x 38 DPI)





BMJ Open **Supplemental figure 3 (a).** QLF patterns in a 75-year-old female patient with IPF: (A) coronal HRCT integers; (B) axial HRCT images. QLF changes were 1% and 25.32 mL at Week 24. QLF score annotated by blue and red dots. The changes of 1% and ≥ 20 mL represent the minimum sensitivity requirements. Whole lung volume was 3414 mL at baseline and 3316 HL & Week 24 in the



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Variable	Category	Combined group (Study 049 + Study 067) (N=190)	Study 049 (n=89)	Study 067 (n=101)
Age, y	Median (range)	68 (46-82)	68 (47–82)	68 (46-80)
Weight, kg			89.1 (56.8–	
	Median (range)	86.3 (46–127.6)	121.8)	82.7 (46–127.6)
Time since first				
IPF diagnosis, y	Median (range)	1.1 (0–6.0)	1.5 (0.1–6.0)	0.9 (0.0-4.9)
Lung function				
FVC, L	Median (range)	2.62 (1.28-5.51)	2.53 (1.32–5.51)	2.78 (1.28-4.45)
FVC, %	Median (range)	69.5 (42.6–	65.9 (42.6–	71.8 (53.9–
predicted		111.7)	111.7)	102.1)
DLCO, % predicted	Median (range)	49.8 (28.2–94.5)	47.4 (30.4–94.5)	53.6 (28.2–85.9)
FEV ₁ /FVC ratio	Median (range)	0.82 (0.65-0.95)	0.83 (0.65-0.94)	0.81 (0.66-0.95)
HRCT ^a				
Whole lung	Median (range)	3.91 (1.52-6.49)	3.57 (2.40-6.49)	4.09 (1.52-6.33)
volume, L				
QLF, %	Median (range)	15 (2–52)	18 (2–51)	13 (2–52)
QLF, mL	Median (range)	559.65 (66.02-	619.31 (66.02–	494.94 (86.18–
		2325.50)	2325.50)	1603.94)
GAP ^b				
GAP score	Median (range)	4 (0-7)	4 (1–7)	4 (0-6)

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			BMJ Open	
Symptom				
Score				
SGRQ	Median (range)	42.5 (0.8-86.4)	45.6 (11.3-81.4)	40.3 (0.8-86.4)
LICSD_SOBO	Median (range)	30.0(1.0-85.0)	30.0(2.1-85.0)	31.0 (1.0_83.0)

DLCO, diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in 1 second; FVC, forced main a capacity; GAP, DLCO, diffusing capacity for carbon monoxide, FDV1, forect explanately gender, age, physiology; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosts DLF, quantitative lung fibrosis; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UCSD-SOBQ, University California San Diego, Shortness of Breath Questionnaire. ^aComputer-assisted QLF scores were derived from volumetric scans of the whole lung. ^b Gender-Age-Pulmonary (GAP) function score. La tomograp. Respiratory Quesi. rom volumetric scans of the white score.

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	Cha	nges in QLF score (%),
		mean (SD)	
	Week 2	24	
		SGRQ stable	SGRQ worsened
	SGRQ improved	(-5 to 5),	(≥5),
	(≤-5), n=48	n=63	n=41
ppFVC improved	n=5	n=11	n=4
(≥3.4%), n=20	-1.6 (3.71)	-1.3 (3.98)	0.5 (0.58)
ppFVC stable	n=31	n=36	n=17
(-3.4% to 3.4%),	0.9 (2.94)	0.5 (3.75)	2.1 (3.04)
n=84			
ppFVC worsened	n=12	n=16	n=20
(≤-3.4%), n=48	2.3 (2.42)	1.7 (3.32)	8.1 (8.27)
	Week 4	18	

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		SGRQ stable	SGRQ worsened
	SGRQ improved	(-5 to 5),	(≥5),
	(≤-5), n=40	n=54	n=39
ppFVC improved	n=5	n=11	n=3
(≥3.4%), n=19	-3.4 (6.50)	0.6 (2.11)	0.7 (1.53)
ppFVC stable	n=24	n=23	n=15
(-3.4% to 3.4%),	0.3 (3.65)	2.5 (4.31)	1.9 (4.09)
n=62			
ppFVC worsened	n=11	n=20	n=21
(≤-3.4%), n=52	1.9 (3.27)	5.5 (5.90)	7.9 (7.37)

 ppFVC, percent-predicted forced vital capacity; QLF, quantitative lung fibrosis; SD, standard deviation; SG, St. George's Respiratory Questionnaire.

Note: mean QLF changes when patients experienced discordance of symptoms were calculated as follows For worsening of one parameter, mean QLF change at Week $24 = (4 \times 0.5\% + 17 \times 2.1\% + 12 \times 2.3\% + 16 \times 1.7\%)/(4 + 17 + 12 + 16) = 1.8\%$ fmean QLF change at Week $48 = (3 \times 0.7\% + 15 \times 1.9\% + 11 \times 1.9\% + 20 \times 5.5\%)/(3 + 15 + 11 + 20) = 3.3\%$. For improvement of one parameter, mean QLF change at Week $24 = (11 \times -1.3\% + 4 \times 0.5\% + 31 \times 0.9\% + 12 \times 2.3\%)/(11 + 4 + 31 + 12) = 0.7\%$; mean QLF change at Week $28 = (11 \times 0.6\% + 3 \times 0.7\% + 24 \times 0.3\% + 11 \times 1.9\%)/(11 + 3 + 24 + 11) = 0.8\%$.

Note: The discordant changes when one parameter worsened were associated with the mean QLF changes of pproximately 2%; discordant changes with one parameter improved were associated with QLF changes of approximately within $\pm 1\%$,

 BMJ Open BMJ Open Supplemental table 3. Relationship of QLF as a percentage and a volume with MCID of SGRQ and pperformed by Copyright, inclusion of the second sec

							Weels 24				<u>c</u>		<u>.</u>		
	1			SCDO			Week 24					החי	2		
		Unadjusted Adjusted Unadjusted Adjusted analysis mean (95% CD) (95% CD)			Unadjusted analysis		Adjusted analysis, ana mean d a D (95% CDS) a 2			sted is	Adjusted analysis, mean (95% CI)				
	N	QLF change, % mean (95% CI)	ES	QLF change, % mean (95% CI)	QLF change, mL mean (95% CI)	ES	QLF change, mL mean (95% CI)	N	QLF change, % mean (95% CI)	ES	QLF change, % mean (95% CI)a	Willogued Ingit	QLF hange, mL mean \$% CI)	ES	QLF change, mL mean (95% CI)
Combined gr	roup						4					<u>s</u> si s			
Worsened ^a	41	4.88 (3.46, 6.30)	1.08	4.39 (2.97, 5.81)	111.94 (77.60, 146.28)	1.03	90.81 (56.47, 125.15)	49	4.55 (3.27, 5.83)	1.02	3.56 (2.28, 2 4.84)		01.90 70.30, 33.49)	0.93	64.67 (33.07, 96.26)
Stable ^a	63	0.49 (-0.66, 1.64)	0.11	0 (-1.15, 1.15)	21.13 (-6.58, 48.83)	0.19	0 (-27.71, 27.70)	86	0.99 (0.02, 1.96)	0.22	0 به (–0.97, و 0.97)	Sumo at	37.23 13.38, 51.08)	0.33	0.00 (-23.85, 23.85)
Improved ^a	48	$ \begin{array}{r} 1.00 \\ (-0.32, \\ 2.32) \end{array} $	0.22	0.51 (-0.81, 1.83)	31.27 (-0.47, 63.01)	0.29	10.14 (-21.60, 41.88)	20	$ \begin{array}{c} -1.00 \\ (-3.01, \\ 1.01) \end{array} $	-0.23	-1.99 (-4.00, 0.02)		18.46 67.92, 30.99)	0.17	-55.69 (-105.15, -6.24)
Study 049													5		
Worsened ^a	22	6.59 (4.16, 9.02)	1.21	6.38 (3.95, 8.81)	137.19 (82.92, 191.45)	1.12	124.14 (69.87, 178.40)	22	6.50 (4.12, 8.88)	1.21	5.23 (2.85, 7.61)		29.62 76.20, 83.05)	1.08	91.92 (38.50, 145.35)
Stable ^a	29	0.21 (-1.91, 2.32)	0.04	0 (-2.12, 2.11)	13.05 (-34.22, 60.31)	0.11	0 (-47.27, 47.26)	44	1.27 (-0.41, 2.95)	0.23	0 (-1.68, 1.68)	o ar a nac	\$7.70 -0.08, 5.48)	0.30	0.00 (-37.78, 37.78)
Improved ^a	22	1.27 (-1.15, 3.70)	0.23	1.06 (-1.36, 3.49)	30.96 (-23.30, 85.23)	0.25	-17.91 (-36.65, 72.18)	8	-2.63 (-6.56, 1.31)	-0.56	-3.90 (-7.83, 0.04)	(-) (-) (-)	59.52 448.12, 9.08)	0.56	-97.22 (-185.82, 8.62)
Study 067												<u> </u>			
Worsened ^a	19	2.89	0.98	2.15	82.71	0.93	54.69	27	2.96	1.00	2.27		79.30	0.85	42.56
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C4 - 1-1 - 9	24	4.32)	0.24	3.58)	125.65)	0.20	97.63)	42	4.14)	0.22	<u>3.45) 6</u>	(0.38)	0.20	79.76)
Stable	34	0.74	0.24		28.02	0.30		42	0.69	0.23		9 7 01	0.39	
		(-0.33, 1.80)		(-1.07, 1.06)	(-4.08, 60.12)		(-32.10, 32.10)		(-0.23, 1.63)		$(-0.94, \mathbf{G})$	6 (101,		(-29.73)
Improveda	26	0.77	0.25	0.03	31.53	0.35	3 51	12	0.08	0.03		<u></u>	0.10	_27.73
mproved	20	(-0.45)	0.25	(-1.19	(-5.18)	0.55	(-33.2)	12	(-1.68	0.05	(-2.37)		0.10	(-83.44)
		1 99)		1 25)	68 24)		40.22)		1.84)		115	ng 40.70,		27 78
		1.57)	1	1.20)	00.21)		Week 48	I	1.01)			9 02) 9 02		27.70)
				SGRO)						FV@			
		Unadjus analys	sted is	Adjusted analysis, mean	Unadju analy	isted sis	Adjusted analysis, mean		Unadju analy	ısted ⁄sis	Adjustedo analysis, o mean	ent Super Su	sted sis	Adjuste analysi mean
	N		ES	$\frac{(95\% \text{ CI})}{\text{OLE}}$	OLE	FS	$\frac{(95\% \text{ CI})}{\text{OLE}}$	N	OLE	БС			БС	(95%) C
		QLF	ES		QLF	ES	QLF		QLF	ES	Change H		E9	QLF change
					mI		mI				دnange, ۵ %⊐			mL
		70 mean		70 mean	mean		mean		70 mean		mean D	S mean		mean
				mean	mean		mean		mean					incan
		(95% (°I)		1 (95% CD	(95%)		(95% CD		(95%)		(95% CDā	•(95% CD		1 (95% C
		(95% CI)		(95% CI)	(95% CI)		(95% CI)		(95% CI)		(95% CI)ჲ́ >	·(%% CI)		(95% C
Combined g	roup	(95% CI)		(95% CI)	(95% CI)		(95% CI)		(95% CI)		(95% CI)¤ ≥ 1	•(%% CI)		(95% C
Combined g Worsened ^a	roup 42	(95% CI) 5.52	1.01	(95% CI) 2.30	(95% CI) 157.32	1.17	(95% CI) 80.75	53	(95% CI) 5.75	1.14	(95% CI) <u>¤</u> ≥ 4.27 m	•(95% CI) 5 55.99	1.18	(95% C
Combined g Worsened ^a	roup 42	(95% CI) 5.52 (3.82,	1.01	(95% CI) 2.30 (0.60,	(95% CI) 157.32 (115.54,	1.17	(95% CI) 80.75 (38.97,	53	(95% CI) 5.75 (4.37,	1.14	(95% CI) 4.27 (2.89, ng	•(%% CI) • • • • • • • • • • • • •	1.18	(95% C 107.61 (71.14
Combined g Worsened ^a	roup 42	(95% CI) 5.52 (3.82, 7.23)	1.01	(95% CI) 2.30 (0.60, 4.01)	(95% CI) 157.32 (115.54, 199.10)	1.17	(95% CI) 80.75 (38.97, 122.53)	53	(95% CI) 5.75 (4.37, 7.14)	1.14	(95% CI) <u>a</u> 4.27 (2.89, ng 5.66) a	•(%5% CI) • • • • • • • • • • • • •	1.18	(95% C 107.61 (71.14 144.07
Combined g Worsened ^a Stable ^a	roup 42 54	(95% CI) 5.52 (3.82, 7.23) 3.22	1.01	(95% CI) 2.30 (0.60, 4.01) 0	(95% CI) 157.32 (115.54, 199.10) 76.57	0.57	(95% CI) 80.75 (38.97, 122.53) 0	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48	0.29	(95% CI)a A training (2.89, g 5.66) and 0.00 d	•(95% CI) 9 155.99 (19.52, 192.45) 9 48.38	0.36	(95% C 107.61 (71.14 144.07 0.00
Combined g Worsened ^a Stable ^a	roup 42 54	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72,	1.01 0.58	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50,	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72,	0.57	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85,	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20,	0.29	(95% CI) 4.27 (2.89, gg 5.66) and 0.00 sig (-1.28, sig	•(%% CI) 9 155.99 (19.52, 192.45) 948.38 C14.67,	1.18 0.36	(95% C 107.61 (71.14 144.07 0.00 (-33.71
Combined g Worsened ^a Stable ^a	roup 42 54	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73)	1.01 0.58	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42)	0.57	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85)	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76)	0.29	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, similar 1.28)	•(%% CI) 9 355.99 (19.52, 192.45) 9 48.38 6 14.67, 82.09)	0.36	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71)
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39	1.01 0.58 0.07	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14	1.17 0.57 0.17	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65	1.14 0.29 -0.14	(95% CD 4.27 (2.89, g 5.66) an 0.00 d (-1.28, similar 1.28) an 1.28) an 1.28 a	•(%% CI) 9 55.99 (19.52, 192.45) 9 14.67, 82.09) u16.46	1.18 0.36	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34,	1.01 0.58 0.07	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56,	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15,	1.17 0.57 0.17	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72,	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90,	1.14 0.29 -0.14	(95% CI) 4.27 (2.89, gg 5.66) and (-1.28, initial 1.28) initial -2.13 (-4.38, cc)	•(%%% CI) 9 9 155.99 (19.52, 192.45) 9 18.38 6 14.67, 72.09) 16.46 (\$\$75.81,	1.18 0.36 	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12)	1.01 0.58 0.07	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42)	1.17 0.57 0.17	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15)	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60)	1.14 0.29 -0.14	(95% CD 4.27 (2.89, g 5.66) and (-1.28, and (-1.28, and (-1.28, and (-4.38, cc, 0.12) and	•(95% CI) 9 9 155.99 (19.52, 192.45) 948.38 C14.67, 82.09) u16.46 (e.75.81, 42.90)	1.18 0.36 - 0.13	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48)
Combined g Worsened ^a Stable ^a Improved ^a Study 049	roup 42 54 41	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12)	1.01 0.58 0.07	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42)	1.17 0.57 0.17	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15)	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60)	1.14 0.29 -0.14	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, milar (-4.38, children (-4.38, 0.12) 00	•(95% CI) = = = = = = = = = = = = =	1.18 0.36 0.13	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48)
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Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a	roup 42 54 41 23	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 3.56)	1.01 0.58 0.07 0.91	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 2.50)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 22.01	1.17 0.57 0.17 1.03	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 12.76,	53 62 20 33	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, (4.78,	1.14 0.29 -0.14 1.24	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, similar (-4.38, chmologies, 0.12) of the second seco	•(95% CI) = = = = = = = = = = = = =	1.18 0.36 	(95% C 107.61 (71.14 144.07 0.00 (-33.71) -64.84 (-124.1 -5.48) 169.32 (114.61
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a	roup 42 54 41 23	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59)	1.01 0.58 0.07 0.91	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60)	1.17 0.57 0.17 1.03	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73)	53 62 20 33	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62)	1.14 0.29 -0.14 1.24	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, similar (-4.38, 0.12) 5.97 (4.05, 5.97 (4.05, 5.97) (4.05, 5.97	•(95% CI) 97 97 97 97 97 97 97 97 97 97	1.18 0.36 - 0.13 1.18	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48) 169.32 (114.61 224.03
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81 (2.2)	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78) 0 (2.00)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (42.52)	1.17 0.57 0.17 1.03 0.67	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (.51)	53 62 20 33 22	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (1.22)	1.14 0.29 -0.14 1.24 0.14	(95% CI) 4.27 (2.89, g, 5.66) a 0.00 (-1.28, milar (-4.38, c 0.12) 5.97 (4.05, 7.89) 0.00 (-2.25)	•(%% CI) = = = = = = = = = = = = =	1.18 0.36 0.13 1.18 0.08	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48) 169.32 (114.61 224.03 0.00 (
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	(95% CI) 5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81 (2.21, 7.13)	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78) 0 (-2.60, 2.30 (-2.60, -2.	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41)	1.17 0.57 0.17 1.03 0.67	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, (-66.54)	53 62 20 33 22	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 2.62)	1.14 0.29 -0.14 1.24 0.14	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, milar (-4.38, children technologies (-4.38, children technologies 5.97 (4.05, s. 7.89) 0.00 (-2.35, children technologies (-2.35, children technologies)	•(%% CI) = = = = = = = = = = = = =	1.18 0.36 - 0.13 1.18 0.08	(95% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48) 169.32 (114.61 224.03 0.00 (-67.01 (-67.01)
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81 (2.21, 7.41)	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78) 0 (-2.60, 2.60)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41)	1.17 0.57 0.17 1.03 0.67	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54)	53 62 20 33 22	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08)	1.14 0.29 -0.14 1.24 0.14	(95% CD2 4.27 (2.89, g, 5.66) and (-1.28, milar (-1.28, milar (-4.38, chindo 0.12) 000 (-2.35, 7.89) 0.00 (-2.35, 2.35)	•(%% CI) = = = = = = = = = = = = =	1.18 0.36 - 0.13 1.18 0.08	$\begin{array}{c} (95\% \ C \\ \hline 107.61 \\ (71.14 \\ 144.07 \\ 0.00 \\ (-33.71 \\ 33.71 \\ -64.84 \\ (-124.1 \\ -5.48) \\ \hline 169.32 \\ (114.61 \\ 224.03 \\ 0.00 \\ (-67.01 \\ 67.00) \\ \hline \end{array}$
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 54 41 23 26 17	(95% CI) 5.52 $(3.82, 7.23)$ 3.22 $(1.72, 4.73)$ 0.39 $(-1.34, 2.12)$ 5.83 $(3.06, 8.59)$ 4.81 $(2.21, 7.41)$ -0.59 (-2.80)	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78) 0 (-2.60, 2.60) -5.40 (95% CI)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41) -20.49	1.17 0.57 0.17 1.03 0.67	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54) -130.36	53 62 20 33 22 11	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08) -1.73	1.14 0.29 -0.14 1.24 0.14 -0.35	(95% CI) 4.27 (2.89, g, 5.66) and (-1.28, similar (-4.38, chan (-4.38, chan (-2.35, chan (-2.46) (-5.78)	•(%% CI) = = = = = = = = = = = = =	1.18 0.36 0.13 1.18 0.08	$\begin{array}{c} (95\% \ C \\ \hline \\ 107.61 \\ (71.14 \\ 144.07 \\ 0.00 \\ (-33.71 \\ 33.71) \\ \hline \\ -64.84 \\ (-124.1 \\ -5.48) \\ \hline \\ 169.32 \\ (114.61 \\ 224.03 \\ 0.00 \\ (-67.01 \\ 67.00) \\ \hline \\ -62.90 \\ (-57.61 \\ -52.90 \\ -62.90 \\ (-57.61 \\ -57$
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26 17	(95% CI) 5.52 $(3.82, 7.23)$ 3.22 $(1.72, 4.73)$ 0.39 $(-1.34, 2.12)$ 5.83 $(3.06, 8.59)$ 4.81 $(2.21, 7.41)$ -0.59 $(-3.80, 2)$	1.01 0.58 0.07 0.91 0.75 - 0.09	(95% CI) 2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83 (-4.56, -1.10) 1.02 (-1.75, 3.78) 0 (-2.60, 2.60) -5.40 (-8.61, -2.61, -2.61, -2.83	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41) -20.49	1.17 0.57 0.17 1.03 0.67 0.13	(95% CI) 80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54) -130.36 (-212.65, 40.72)	53 62 20 33 22 11	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08) -1.73 (-5.05, (-5.05,	1.14 0.29 -0.14 1.24 0.14 -0.35	(95% CD) 4.27 (2.89, g, 5.66) and (-1.28, similar (-1.28, similar (-2.13, similar (-2.35, similar (-5.78, similar (-5.78, similar)	•(%% CI) = = = = = = = = = = = = =	1.18 0.36 0.13 1.18 0.08 0.36	$\begin{array}{c} (95\% \ C \\ \hline \\ 107.61 \\ (71.14 \\ 144.07 \\ 0.00 \\ (-33.71 \\ 33.71 \\ \hline \\ 33.71 \\ \hline \\ -64.84 \\ (-124.1 \\ -5.48 \\ \hline \\ (-124.1 \\ -$

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6	Study 067												ing		
7	Worsened ^a	19	5.16	1.26	3.41	144.57	1.65	98.92	20	4.20	0.96	2.30	a T 13.39	1.16	45.26
8			(3.18,		(1.43,	(102.25,		(56.6,		(2.16,		(0.26,	č 6 7.81,		(-0.32,
9			7.14)		5.39)	186.90)		141.25)		6.24)		4.34)			90.84)
10	Stable ^a	28	1.75	0.42	0	45.65	0.51	0	40	1.90	0.42	0.00	S S S S S S S S S S	0.68	0.00
11			(0.12,		(-1.63,	(10.78,		(-34.87,		(0.46,		(-1.44,	e ig ig 5.90,		(-32.23,
12			3.38)		1.63)	80.51)		34.86)		3.34)		1.44)	e <u>10</u>0.36)		32.23)
13	Improved ^a	24	1.08	0.26	-0.67	52.33	0.59	6.68	9	0.67	0.17	-1.23	to P 25.06	0.28	-43.07
14	-		(-0.68,		(-2.43,	(14.67,		(-30.98,		(-2.38,		(-4.28,	t v 342.90,		(-111.03,
15			2.85)		1.10)	89.99)		44.34)		3.71)		1.81)	작 등 <u>@</u> 3.01)		24.88)

Note: Negative sign denotes decline in ppFVC. predicted forced vital capacity; QLF, quantitative lung fibrosis; SGRQ, St. George's Respiratory Question 2012 ^aWorsened: SGRQ change ≥ 5 points or ppFVC change $\leq -3.4\%$; stable: SGRQ change between -5 and 5 boints or ppFVC change between -3.4% and 3.4%; improved: SGRQ change ≤ -5 points or ppFVC change $\geq 3.4\%$.

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Minimum clinically important difference in Quantitative Lung Fibrosis score associated with all-cause mortality in idiopathic pulmonary fibrosis: subanalysis from two phase II trials of pamrevlumab

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2 3 4 5	1	Minimum clinically important difference in Quantitative Lung Fibrosis score
5 6 7	2	associated with all-cause mortality in idiopathic pulmonary fibrosis:
8 9 10	3	subanalysis from two phase II trials of pamrevlumab
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13 14 15	5	Grace Hyun J Kim, ¹ Xueping Zhang, ² Matthew S Brown, ¹ Lona Poole, ² Jonathan G Goldin ¹
15 16 17	6	
18 19	7	¹ David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;
20 21 22	8	² FibroGen, Inc., San Francisco, CA, USA
22 23 24	9	
25 26	10	Corresponding author:
27 28 20	11	Grace Hyun J Kim, PhD, MS
29 30 31	12	Professor-in-Residence
32 33	13	Co-director, Center for Computer Vision and Imaging Biomarkers
34 35 36	14	Department of Radiological Sciences
37 38	15	David Geffen School of Medicine at UCLA
39 40	16	Department of Biostatistics Fielding School of Public at UCLA
41 42 43	17	924 Westwood Blvd, Suite 650
44 45	18	Los Angeles, CA 90024 USA
46 47	19	E-mail: gracekim@mednet.ucla.edu
48 49 50	20	ORCID: 0000-0003-1225-3489
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ABSTRACT (300/300 words)

6	31	
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8	32	Objectives: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease. Chest
9		
10 11	33	high-resolution computed tomography (HRCT) is instrumental in IPF management, and the
12		
13	34	Quantitative Lung Fibrosis (QLF) score is a computer-assisted metric for quantifying lung
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15	35	disease using HRCT. The aim is to assess the change in QLF score associated with a minimum
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17	36	clinically important difference (MCID) of IPF symptoms and physiologic lung function, and also
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19	37	determine the MCID of QLF change associated with all-cause mortality to serve as an imaging
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21	38	biomarker to confirm disease progression and response to therapy
22	50	etentation to continuit alsoase progression and response to alonapy.
23	30	Design and Study setting: We conducted <i>post hoc</i> analyses of prospective data from two IPF
25	55	besign and study setting. We conducted post not analyses of prospective data from two if i
26	40	Phase II studies of namraylymah, a fully human monoclonal antibody that hinds to and inhibits
27	40	
28	4.4	compositive tiggue growth factor activity
29	41	connective tissue growth factor activity.
30		
31	42	Participants: Overall, 152 patients with follow-up visits after week 24.
32 22		
33	43	Methods: We used the anchor-based Jaeschke's method to estimate the MCID of the QLF score
35		
36	44	that corresponded with the already established MCID of St. George's Respiratory Questionnaire
37		
38	45	(SGRQ) and percent-predicted forced vital capacity (ppFVC). We also conducted a Cox
39		
40	46	regression analysis to establish a sensitive and robust MCID of the QLF score in predicting all-
41		
42	47	cause mortality.
43 44		
44	48	Results: QLF changes of 4.4% and 3.6% corresponded to the established MCID of 5-point
46		
47	49	increase in SGRO and a 3.4% reduction in ppFVC, respectively. OLF changes of 1%(HR=4.98,
48	-	
49	50	p=0.05) 2%(HR=4.04 $p=0.041$) 20 mL(HR=6.37 $p=0.024$) and 22 mL(HR=6.38 $p=0.024$)
50	50	p = 0.00, $p = 0.01$, $p = 0.01$, $p = 0.01$, $p = 0.02$, $p =$
51	51	predicted mortality
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Conclusion: A conservative metric of 2% can be used as the MCID of QLF for predicting allcause mortality. This may be considered in IPF trials in which the degree of structural fibrosis assessed via HRCT is an endpoint. The MCID of SGRQ and FVC correspond with a greater amount of QLF and may reflect that a greater amount of change in fibrosis is required before there is functional change.

58 Trial registration: NCT01262001, NCT01890265

60 Strengths and limitations of this study

This study demonstrates the utilization of an anchor-based approach and an early prediction
of mortality in estimating a minimum clinically important difference (MCID).

▶ This study estimates the MCID for extent pulmonary fibrosis in Idiopathic pulmonary fibrosis

64 (IPF), using high-resolution CT (HRCT) as an imaging biomarker based on two clinical trials, in

65 which subjects underwent HRCT scans according to clinical protocols – reducing the potential

66 bias compared to observational data.

▶ The limitation of this study is that the MCID estimation was based on *post hoc* research of

68 using the existing data from clinical trials.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive interstitial lung disease that includes symptoms of cough, worsening of dyspnoea, and progressive lung injury and scarring. Together, these symptoms limit physical activity and reduce patient health-related quality of life (HRQOL) [1–3]. There is no cure for IPF [3], and its prognosis is very poor. Median survival is estimated to be no more than 2–5 years after diagnosis [4]. Two approved antifibrotic drugs (pirfenidone and nintedanib) significantly reduce the rate of lung-function decline in IPF [5–7]. However, individual responses to treatment are variable and unpredictable, and HRQOL does not improve [6,7]. Identifying individual small, detectable, and clinically meaningful changes of patient-level correlation will be beneficial for both physicians and patients in making informed decisions for available antifibrotic treatments and for on-going novel therapeutic discovery in clinical trials. Pamrevlumab is a fully human monoclonal antibody that binds to and inhibits the activity of connective tissue growth factor [8-10]. Two phase II studies, one open-label and the other placebo-controlled intravenous administration of pamrevlumab, demonstrated slowing the rate of lung-function decline, progression of lung fibrosis evident on computed tomography (CT), and a trend toward improved HRQOL. Adverse events were generally mild [9,10]. However, a recent

Phase III trial of pamrevlumab for IPF (ZEPHYRUS-1) did not meet its primary endpoint of absolute change in forced vital capacity (FVC) from baseline to week 48 [11, 12]. Its companion study (ZEPHYRUS-2) was terminated [13].

IPF treatment options are limited, and improved monitoring and a sensitive metric for assessing therapeutic efficacy are needed. Radiologically detected lung fibrosis correlates with physiologic

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lung function and symptomatic changes in IPF, and early and sensitive imaging biomarkers are 94 needed to confirm disease progression or worsening of FVC and response to therapy as quickly 95 as possible to optimise drug development and patient care [2,3,14–17]. 96

FVC is the most common measure for assessing treatment efficacy in IPF [18,19]. HROOL and 98 99 other patient-reported outcome (PRO) measures are also important endpoints for evaluating disease progression and treatment efficacy including St. George's Respiratory Questionnaire 100 (SGRQ) [3,20]. Use of chest high-resolution CT (HRCT) is expanding and is instrumental in the 101 102 diagnosis and management of IPF [1]. Computer-assisted methods for quantifying lung disease on HRCT calculate textural features derived from image data and classify different patterns of 103 interstitial lung diseases based on machine learning algorithms [21–23]. Computational 104 quantitative scoring systems that analyse HRCT images have been used as imaging biomarkers 105 in IPF clinical trials to assess the degree and progression of structural lung fibrosis. Of these, 106 Quantitative Lung Fibrosis (QLF) has demonstrated high reproducibility [22–24] (figure 1). 107 QLF is associated with more prospective validation than other quantitative CT techniques and 108 has been used in recent clinical trials of IPF [21,25]. In two phase 2 IPF trials of pamrevlumab, 109 significant correlations were observed between QLF changes and the changes in percent-110 predicted FVC (ppFVC) (ranging from -0.51 to -0.64), as well as with changes in PRO, SGRQ 111 (ranging from 0.27 to 0.30) [9, 10, 26]. Furthermore, QLF changes of <2% were associated with 112 113 better long-term survival than changes $\geq 2\%$ for patients with interstitial lung disease in 114 scleroderma [27]. 115

The minimum clinically important difference (MCID) is an important standard for determining meaningful changes related to a clinical intervention or measurement tool [28] and represents the smallest detectable and beneficial change [29]. Both distribution-based methods (using variations from repeated measures) and anchor-based approaches (relying on established MCIDs from other relevant clinical variables) are used to determine MCIDs [30]. The MCID of QLF changes in an IPF cohort has not been evaluated. For clinically meaningful validation, an MCID of the QLF threshold should provide a tool for both identifying an effective treatment and detecting a difference in mortality over time. This is especially important in IPF, which is a progressive disease with a considerably shorter median survival than other chronic lung diseases [31]. Our aim is to assess the change in QLF score associated with MCID of a PRO measure, SGRQ, and a key measure in lung function physiology, FVC, using the anchor-based Jaeschke's method, and to determine the MCID of QLF change based on its association with all-cause mortality through a *post hoc* analysis of prospective data from two Phase II studies of pamrevlumab, exploring the potential of QLF as an imaging marker to confirm disease progression and response to therapy.
1 2		
3 4	132	METHODS
5 6	133	
7 8	134	Patients
9 10 11	135	This was a secondary analysis of study 049 [9] and the Phase II PRAISE study [10]. The two
12 13	136	study populations were pooled to include a total of 190 patients with IPF. Eligibility criteria for
14 15	137	the two studies were similar [9,10]. Study 049 (NCT01262001), conducted between March 2011
16 17 18	138	and December 2012 at 18 centres in the United States, was a single-arm, open-label study [9].
19 20	139	Pamrevlumab was administered every 3 weeks for 45 weeks: Cohort 1 received 15 mg/kg and
21 22	140	Cohort 2 received 30 mg/kg [9]. PRAISE (Study 067 [NCT01890265]), conducted between
23 24	141	August 2013 and July 2017 at 39 centres throughout North America, Australia, Africa, and
25 26 27	142	Europe, was a double-blind, placebo-controlled study [10]. Patients were randomised to receive
28 29	143	placebo or pamrevlumab 30 mg/kg every 3 weeks for 45 weeks [10].
30 31	144	Local ethics committees / institutional review boards (ECs/IRBs) approved the protocol for each
32 33 24	145	site, and all patients provided written informed consent before enrollment (Study 049:
35 36	146	Aspire IRB00004587; Study 067 (PRAISE): Quorum (now Advarra) 00023875; both studies
37 38	147	WIRB (now WCG IRB) IRB00000533).
39 40	148	
41 42 43	149	Of the 190 patients, 155 had follow-up visits after Week 24 and data from Week-48 visits,
44 45	150	including the primary outcome measure of FVC. For both studies, pulmonary function tests,
46 47	151	including spirometry, were performed at baseline and every 12 weeks thereafter, and HRCT was
48 49	152	performed at baseline and every 24 weeks. SGRQ was completed at baseline and Weeks 24 and
50 51 52	153	48. Mortality data were collected for the lengths of the respective studies.
53 54	154	
55 56	155	Patient and public involvement
57 58		8
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No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this study.

Outcomes

QLF scores were estimated from standardised non-contrast thin-section volumetric HRCT scans using an established radiomic texture-based quantification algorithm. QLF uses image normalization (denoising) to minimise cross-site variability within images prior to texture calculation [22]. QLF was measured as extent (%) and volume (mL). Supplemental figure 1 provides an example of QLF extent (%) and volume (mL) on HRCT and overlaid images for a patient with IPF. QLF measures the amount of reticulation with architectural distortion in the lung. Scores range from 0–100% for extent of fibrosis and from 0 mL to total lung capacity for volume of fibrosis. Greater scores represent increased fibrosis [10,21]. For this analysis, we considered 24-Week or 48-Week changes in QLF in the whole lung, which were calculated from the QLF scores of baseline HRCT.

Estimation of a Minimum Clinically Important Difference

We used the anchor-based Jaeschke's method with predefined criteria for establishing the MCID of QLF that corresponded with the established MCIDs of SGRQ and ppFVC. We used a landmark Cox proportional hazards regression analysis using all-cause mortality as an anchor by applying several thresholds of 24-Week QLF changes. Patients did not have follow-up visits if they died or received a lung transplant.

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178	The SGRQ is a self-administered questionnaire that assesses HRQOL in respiratory diseases.
179	SGRQ total score ranges from 0-100, and greater scores indicating deterioration in HRQOL
180	and in this study SGRQ was used to represent severity of symptoms. The MCID of the SGRQ
181	was assumed to be ± 5 points [32]. Changes in FVC are often used as primary endpoints in trials
182	of respiratory diseases. The ppFVC is an estimate of lung function, with greater percentages
183	indicating better function. The MCID of ppFVC was assumed to be $\pm 3.4\%$ [33]. In this study,
184	SGRQ was used to represent severity of symptoms, and lung function, respectively.
185	
186	Changes in longitudinal QLF scores were initially correlated with established MCID changes in
187	SGRQ and ppFVC. The anchor-based Jaeschke's method was used to estimate the MCID of
188	QLF scores from these changes in SGRQ and ppFVC from baseline at Weeks 24 and 48.
189	Jaeschke's method describes the mean change in the measurement of interest for patients who
190	experience a change in an anchor [31]. Multiple anchors were chosen to obtain robust, unbiased
191	estimates of the MCID [34]. Another anchor-based Cox proportional hazards regression was
192	used for all-cause mortality, in which duration of survival or time to death was used as an
193	anchor. A preliminary threshold was derived from a previous reproducibility study [35] and six-
194	month change observed in a clinical trial [21]. The reproducibility coefficient of QLF score was
195	estimated to be approximately 0.4% ($\approx 2.77 \times 0.14 = \sqrt{2} \times 1.96 \times 0.14$) [35, 36] and the mean of
196	six-month change was 0.98% for extent QLF and 21.7 mL for volume QLF from a nintedanib
197	arm [21] Thresholds increased incrementally as extent changes of 1, 2, 3, and 4% and volume
198	changes of 20, 22, 24, and 26 mL [21, 35]. Covariates of age and ppFVC at baseline were
199	adjusted in the regression analysis (Of note that the covariates of sex and percent-predicted
200	diffusing Capacity of Lungs for Carbon Monoxide (ppDLCO) were not used in Cox regression

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due to the imbalanced distribution of sex in the multiple thresholds and the collinearity among ppDLCO, ppFVC, and QLF). Continuous-scale and multiple thresholds of QLF scores were compared to test differences in mortality risk. In addition, the MCID from each anchor (SGRQ and ppFVC) was tested in a Cox regression model as a threshold. Summary statistics are reported for demographics and clinical variables. Continuous variables are reported as mean and standard deviation (SD), and categorical variables are reported as ages. frequencies and percentages.

RESULTS

212	
213	There were no notable differences in demographics or baseline characteristics between the
214	cohorts (table 1, supplemental table 1). The median (±Inter Quartile Range) length of the
215	follow-up period was 337 (±504) days. Because changes in QLF outcomes for all-cause
216	mortality were derived from Week-24 data and the screening HRCT scan, the median observed
217	survival was relatively short. In total 185 available screening HRCT scans, 33 patients had no
218	available survival analyses after Week 24 because they discontinued prior to Week-24 visits
219	(N=19), or they died prior to Week 24 (N=13) or did not undergo scan (N=1) (Supplemental
220	figure 2).

		Combined		
Variable	Category	Combined group (Study 049 + Study 067) (N=190)	Study 049 (n=89)	Study 067 (n=101)
Age, y	Mean (SD)	68.1 (7.06)	67.9 (7.04)	68.2 (7.11)
Sex, n (%)	Male	145 (76.3)	71 (79.8)	74 (73.3)
	Female	45 (23.7)	18 (20.2)	27 (26.7)
Race, n (%)	American Indian or		4	
	Alaska Native	1 (0.5)	1 (1.1)	0
	Asian	8 (4.2)	0	8 (7.9)
	Black or African			
	American	1 (0.5)	1 (1.1)	0
	White	172 (90.5)	87 (97.8)	85 (84.2)
	Other	8 (4.2)	0	8 (7.9)
Weight, kg	n	190	89	101
	Mean (SD)	86.40 (16.46)	89.50 (14.82)	83.67 (17.39

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	n	189	89	100
IPF diagnosis, y	Mean (SD)	1.60 (1.35)	1.91 (1.54)	1.32 (1.0
Tobacco	Current	3 (1.6)	0	3 (3.0)
smoking status, n	Former	60 (31.6)	0	60 (59.4
(%)	Never	38 (20.0)	0	38 (37.6
	Missing	89 (46.8)	89 (100.0)	0
Lung function				
FVC, L	n	190	89	101
	Mean (SD)	2.79 (0.78)	2.73 (0.80)	2.84 (0.7
FVC, %	n	190	89	101
predicted	Mean (SD)	70.44 (13.42)	66.79 (14.68)	73.66 (11.
DLCO, %	n	190	89	101
predicted	Mean (SD)	51.38 (13.72)	48.85 (13.32)	53.61 (13.)
FEV ₁ /FVC ratio	n	190	89	101
	Mean (SD)	0.81 (0.06)	0.82 (0.06)	0.80 (0.0
HRCT ^a	0			
Whole lung	n	185	89	96
volume, L	Mean (SD)	3.95 (1.01)	3.81 (0.94)	4.07 (1.0
QLF, %	n	185	89	96
	Mean (SD)	16.8 (10.33)	19.6 (11.20)	14.3 (8.7
QLF, mL	n	185	89	96
	Mean (SD)	622.74 (367.67)	701.13 (395.62)	550.07 (325
GAP ^b		(V)		
GAP score	n	190	89	101
	Mean (SD)	3.8 (1.33)	4.1 (1.33)	3.6 (1.30
Symptom Score				
Symptom Score SGRQ	n	186	88	98
Symptom Score SGRQ	n Mean (SD)	186 44.04 (17.87)	88 46.24 (14.78)	98 42.05 (20.
Symptom Score SGRQ UCSD-SOBQ	n Mean (SD) n	186 44.04 (17.87) 135	88 46.24 (14.78) 89	98 42.05 (20. 46
Symptom Score SGRQ UCSD-SOBQ	n Mean (SD) n Mean (SD)	186 44.04 (17.87) 135 33.10 (20.32)	88 46.24 (14.78) 89 32.13 (18.68)	98 42.05 (20 46 34.98 (23

Anchor-based analyses assessed the relationship between QLF and the established MCIDs for SGRQ, ppFVC (table 2), or both (supplemental table 2). Thresholds of QLF changes (extent and volume) at Week 24 were 4.4% and 91 mL for symptomatic worsening, respectively, when applying Jaeschke's method using SGRQ as an anchor, and 3.6% and 65 mL for worsening lung function, respectively, when using ppFVC as an anchor. For improved condition of symptom by SGRQ or lung function by ppFVC, the thresholds of QLF changes were $\leq 0.5\%$ and 10mL, and -2.0% and -56mL, respectively. At Week 48 for worsened condition, the thresholds of QLF changes were 2.3% and 81mL by SGRQ, and 4.3% and 108mL by ppFVC, respectively, and for improved condition the QLF changes were -2.8% and -54mL by SGRQ, and -2.1% and -65mL by ppFVC, respectively.

Table 2. Relationship of QLF extent (%) and volume (mL) with the anchor-based MCID of

SGRQ and FVC using Jaeschke's method

Anchor		Adjusted corresponding QLF values of thresholds compared with stable condition ^a				
		Weel	x 24	Wee	k 48	
			SGR	Q change		
				U,		
SGRQ	Whole lung	Improved ^b	Worsened	Improved ^b	Worsened ^b	
		(N=48)	b	(N=41)	(N=42)	
			(N=41)			
	QLF, %	≤0.5%	≥4.4 %°	$\leq -2.8\%^{c}$	≥2.3%	
	95% CI	[-1.5, 2.5]	[2.3, 6.5]	[-5.4, -0.2]	[-0.3, 4.9]	
	QLF, mL	≤10 mL	≥91 mL ^c	\leq -54 mL	≥81 mL ^c	
	95% CI	[-38, 58]	[41, 141]	[-118, 9]	[18, 144]	
			ppFV	/C change		
		Improved ^b	Worsened	Improved ^b	Worsened ^b	
		(N=20)	b	(N=20)	(N=53)	
		(11 20)	(N=49)	(1, 20)	(10.55)	

	ppFVC	QLF, %	$\leq -2.0\%$	≥3.6% ^c	$\leq -2.1\%$	≥4.3% ^c
		95% CI	[-4.5, 0.6]	[1.7, 5.4]	[-5.1, 0.8]	[2.1, 6.4]
		QLF, mL	\leq -56 mL	≥65 mL ^c	\leq -65 mL	≥108 mL ^c
		95% CI	[-118, 7]	[20, 110]	[-143, 13]	[51, 164]
245	CI, confide	ence interval; FV	C, forced vital ca	apacity; MCID,	minimum clinica	lly important
246	difference;	ppFVC, percent	t-predicted forced	l vital capacity;	QLF, quantitativ	e lung fibrosis;
247	SGRQ, St.	George's Respi	ratory Questionna	aire.		
248	^a Shifted by	the mean chang	ges at ± 5 points S	GRQ and $\pm 3.4\%$	% ppFVC; stated	with 2 significant
249	figures.					
250	⁰Worsened	I: SGRQ change	\geq 5 points or ppF	VC change ≤ -3	3.4%; stable: SGF	Q change betwee
251	-5 and 5 p	oints or ppFVC	change between –	-3.4% and $3.4%$; improved: SGR	Q change ≤ -5
252	points or p	$pFVC$ change \geq .	3.4%.		. 1.1	1.41 1.00
253	°1wo 95%	Cls of the differ	ence between the	improved and	stable groups and	the difference
254	between w	orse and stable g	groups are not ove	erwrapped. 95%	• CIs were obtain	ed from an one-wa
255	ANOVAn	nodel in the moc	lel. Comparisons	are obtained fro	om the same mode	el using LSMEAN
256	statement.					
257						
250	Acroomon	t baturaan tha tur	a components of	armentana and	lung function and	thair aarraan andi
258	Agreemen	t between the tw	o components of	symptoms and	lung lunction and	their correspondi
250	ahangaa in	OI E saora ara r	concerted in supple	montal table 7	Similar paraante	agas of nationts
259	changes in	QLF Scole ale I	eponed in supple	emental table 2	. Similar percenta	ages of patients
260	evnerience	d concordance i	n changes at Wee	ks 24 and 48 It	f changes in SGR	O and EVC were
200	experience		ii changes at wee	KS 24 and 40. II	changes in SOR	
261	both consid	dered worsened	the mean (SD) cl	nanges in exten	t of OLE were 8.1	% (8 27) at Week
201	both consid	dered worsened,	the mean (SD) er	lianges in exten		70 (0.27) at Week
262	24 and 7 9	% (7 37) at Wee	k 48. If changes y	vere both consi	dered stable, the r	mean (SD) change
202	2-+ und 7.9	/0 (7.57) at wee	k 40. If changes v	were both const		fieddi (BD) endinge
263	in OLE we	ere 0.5% (3.75) a	t Week 24 and 2	5% (4 31) at W	eek 48 If change	s were both
205	m qLi we	ne 0.570 (5.75) d	t Week 24 and 2.	570 (4.51) dt W	eek 40. If endige	s were both
264	considered	limproved the r	nean (SD) change	es in OI E were	-1.6% (3.71) at V	Week 24 and -3.4°
204	considered	i improved, the i	fical (SD) change		1.070 (5.71) at v	Veek 24 and 5.4
265	(6 50) at W	Veek 48 Overall	the concordant of	hanges for wor	sening stability	and improvement
205	(0.50) ut v			indinges for wor	sennig, studnity,	una improvement
266	followed e	xpected direction	nal changes in OI	F scores		
200	iono wea e	Apeeled uncerto				
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268	IPF is a co	mplex disease the	at includes dynar	nic changes in I	lung symptoms, f	unction, and
269	structure o	ver time. These	changes do not al	ways progress a	at the same rate, a	and most patients
270	experience	ed discordance in	symptoms and lu	ung function. T	he discordant cha	nges when one
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parameter worsened were associated with the mean QLF changes of approximately 2%; discordant changes with one parameter improved were associated with QLF changes of approximately within $\pm 1\%$, (supplemental table 2). The relationship of QLF changes to each of the MCIDs of SGRQ and ppFVC are provided in supplemental table 3. Unadjusted analyses demonstrated that mean changes in MCIDs were greater (e.g. 4.88%, 95% CI (3.46, 6.30) vs. 4.39% 95% CI (2.97, 5.81) when applying SGRQ as an anchor at Week 24) compared with the stable group (e.g. 0.49%, 95% CI (-0.31, 2.32) vs. 0.00%, 95% CI (-1.15, 1.15) when applying SGRQ as an anchor) and trended in the correct direction. The effect sizes of QLF changes (both extent and volume) were approximately 1 or slightly greater for patient groups with worsened SGRQ scores and worsened ppFVC (i.e. 1.08 for extent and 1.03 for volume when applying SGRQ as an anchor, 1.02 for extent, and 0.93 for volume when applying ppFVC as an anchor, respectively), indicating a strong relationship between QLF and the anchor parameter. The effect sizes for worsened conditions were greater than those observed for patients with not-worsened conditions (i.e. 0.93, 0.33, -0.17 for worsening, stable, and better in the effect size of QLF volume change, respectively, when applying ppFVC as an anchor).

A Cox proportional hazards regression model of QLF changes is presented in **table 3**. Changes ranging from 1–4% and from 20–26 mL were associated with statistically significant differences in all-cause mortality. A minimum threshold of a 1% change in QLF at Week 24 was associated with an increased risk of death. A two- to five-fold increased risk of death was observed for patients with sizeable changes in QLF (i.e., changes greater than the thresholds established by the single-variable anchor-based analyses). Supplemental figures 3a and 3b present patients

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294	with IPF with QLF changes of 1% (25 mL) and 2% (46 mL), respectively, at Week 24. We used
295	an MCID derived from the increase in SGRQ and the decrease in ppFVC, which indicates of
296	worsening in IPF, from table 2. After applying these thresholds, estimated MCID from QLF
297	changes at Week 24, using all-cause mortality, Cox proportional hazards model revealed a four-
298	to nine-fold increased risk of death for patients with sizeable changes in QLF at Week 24
299	(table 4). Significant differences were observed from 1% to 4% changes (20-26mL for QLF
300	volume) (table 3), whereas 4.4% or 3.6% changes (or 91mL or 65mL) for volume changes)
301	were derived from the changes of QLF corresponding to the anchors of SGRQ and ppFVC,
302	respectively (table 4).
303	

Table 3. Cox proportional hazards model using all-cause mortality as an anchor with QLF

with cutoff of Week 24 changes

QLF changes in whole lung	Total patients (N=152)	Total deaths (n=11) (%)	HR (95% CI)	P -Value
Continuous ⁺ , %			1.20 (1.08, 1.34)	0.001
Continuous ⁺ , mL			1.01 (1.01, 1.02)	<0.001
Week 24	Total patients	Total		
QLF changes in whole lung	meeting listed threshold, n (%)	deaths meeting listed threshold, n (%)	HR (95% CI)	P -Value
≥0%	118 (78)	9 (82)	1.48 (0.31, 7.02)	0.623
≥0 mL	99 (65)	9 (82)	2.57 (0.55, 12.1)	0.232
Thresholds QLF %				
≥1%	101 (66)	9 (82)	4.98 (1.00, 24.8)	0.050
≥2%	87 (57)	8 (73)	4.04 (1.06, 15.4)	0.041

	≥3%					
		66 (43)	6 (55)	4.69 (1.24, 17.7)	0.023	
	≥4%	50 (33)	5 (45)	4.52 (1.18, 17.3)	0.028	
	QLF volume					
	≥20 mL	84 (55)	8 (73)	6.37 (1.27, 32.0)	0.024	
	≥22 mL	83 (55)	8 (73)	6.38 (1.27, 32.0)	0.024	
	≥24 mL	81 (53)	8 (73)	6.83 (1.37, 34.2)	0.019	
	≥26 mL	80 (53)	8 (73)	7.63 (1.51, 38.6)	0.014	
	⁺ : the proportional h CI, confidence inter deviation.	azards assumption be rval; HR, hazard rati	eing examined and o; QLF, quantita	d met using Schoenfield resi tive lung fibrosis; SD, stan	duals. dard	
	Table 4. Anchor-b	ased Cox proportio	onal hazards mo	odel with an MCID derive	ed from	
SGRQ and ppFVC as anchors						
		Total	Tota	Risk of death,	D X7-1	
		Total	Total) Deaths (n	Risk of death, =11) HR (95% CI)	<i>P</i> -Val	
	QLF changes in v	Total (N=155) whole lung by SGR	Total) Deaths (n Q using ±5 as as	Risk of death, =11) HR (95% CI)	<i>P</i> -Val	
	QLF changes in v	Total (N=155) whole lung by SGR 27 (18%	Total) Deaths (n Q using ±5 as as >) 4 (36%)	Risk of death, Image: method HR (95% CI) 0 6.17 (1.63, 23.4)	<i>P</i> -Valu 0.007	
	QLF changes in v ≥4.4% ≥91 mL	Total (N=155) whole lung by SGR 27 (18%) 47 (31%)	Total) Deaths (n Q using ±5 as an (a) 4 (36%) (b) 6 (55%)	Risk of death, HR (95% CI) nchor 6) 6.17 (1.63, 23.4)	<i>P</i> -Val 0.007	
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w	Total (N=155) whole lung by SGR 27 (18%) 47 (31%) hole lung by ppFV(1)	Tota Deaths (n Q using ±5 as an (a) (b) (c) (c) <td>Risk of death, HR (95% CI) nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor</td> <td><i>P</i>-Val 0.00 0.00</td>	Risk of death, HR (95% CI) nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor	<i>P</i> -Val 0.00 0.00	
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w ≥3.6%	Total (N=155) whole lung by SGR 27 (18% 47 (31%) hole lung by ppFV 41 (27%)	Tota Tota) Deaths (n Q using ± 5 as an (a) (b) 4 (36%) (c) 6 (55%) C with $\pm 3.4\%$ a (a) (b) 4 (36%)	Risk of death, HR (95% CI) nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor 6) 4.33 (1.14, 16.5)	<i>P</i> -Val 0.007 0.003	
	QLF changes in v ≥4.4% ≥91 mL QLF changes in w	Total (N=155) whole lung by SGR 27 (18%) 47 (31%) hole lung by ppFV(1)	Tota Deaths (n Q using ±5 as an a) b) 4 (36%) b) 6 (55%) C with ±3.4% a	Risk of death, HR (95% CI) nchor 6) 6.17 (1.63, 23.4) 6) 7.35 (1.98, 27.3) s anchor	<i>P-</i> V	

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DISCUSSION

This study established the MCID for change in QLF score in the setting of IPF as it relates to all-cause mortality. A minimum threshold of change in QLF of 1% or 20 mL at Week 24 was associated with an increased risk of death for patients with IPF. To include changes observed with SGRQ and FVC, a conservative estimate of 2% can be adopted as the MCID of QLF, based on the Week-24 mean QLF changes when patients experienced worsening of either SGRQ or ppFVC. An increased risk of death was also associated with sizeable QLF changes using Jaeschke's method with anchors of IPF symptoms (SGRQ) and lung function (ppFVC) to determine MCID.

Changes in QLF were consistent with changes in SGRQ and ppFVC, and mean QLF changes coincided with both symptom and lung-function changes. Changes in QLF and SGRQ were positively correlated, and changes in QLF and ppFVC were inversely correlated [9, 10, 26]. This indicates that, generally, a responder in IPF clinical trial was associated with a reduction in QLF, a reduction in SGRO, and an increase in ppFVC. The threshold of QLF change for improved symptoms was close to zero (i.e. 0.5%) at Week 24 compared with the reduction (-2.0%) in MCID for improved lung function, but at Week 48, further reduced in both symptomatic changes (i.e. -2.8%) and functional changes (-2.1%) (see table 2 for the details). In contrast, the threshold of QLF change for worsened symptoms had a greater magnitude at Week 24 (i.e. 4.4%) than the threshold for worsened lung function (i.e. 3.6%), but at Week 48, functional changes (i.e. 4.3%) were greater than symptomatic changes (i.e. 2.3%) (see table 2 for the details). This suggests that symptomatic changes (measured by SGRQ) improve slower or more inconsistently than

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functional changes (FVC) for improvement but were sensitive in worsening faster. This is likely 343 a result, in part, of the effects of limited symptom recall and the subjective nature of HRQOL. 344 345 Quantitative HRCT tools for measuring pulmonary fibrosis is a critical in a therapeutic 346 development in ILD to confirm efficacy or evaluate safety of an experimental drug [18, 21, 25]. 347 348 Assessments of QLF change have mostly served as secondary or exploratory quantitative imaging outcomes to estimate changes in lung fibrosis in clinical trials [11, 13, 25]. QLF score 349 based on HRCT images is traceable and can visualise regions of fibrosis. The incremental 350 351 changes in QLF extent (%) or volume (mL) highlight the structural worsening in IPF that is associated with decreased FVC [10]. The incremental worsening in ppFVC from Week 24 and 352 Week 48 confirms that FVC is a reasonably reliable assessment in IPF and supports its use as the 353 primary efficacy endpoint in clinical trials [19]. A role of quantitative tools in future can be 354 expanded in patient care using digital AI platform, when a trial is approved with a positive 355 outcome from a primary endpoint or a secondary endpoint of an imaging outcome. 356 357 In this post hoc analysis of prospective IPF clinical trial data, an anchor-based method was used 358 359 to estimate the threshold of QLF change associated with established MCIDs of SGRQ and ppFVC, and a sensitivity-based method was used to establish the MCID of QLF from all-cause 360 361 mortality. Sensitivity-based methods for estimating MCID ideally require a baseline variable or 362 characteristic to reliably quantify disease severity. For HRCT-based QLF, this requires repeat HRCT scans in a coffee break-type (i.e., approximately 15 minutes) [37,38] of experiment for 363 364 patients with IPF, but this method poses ethical challenges because of the unnecessary risk of 365 radiation exposure. The variability can be estimated statistically [25], but we recognise this as a

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limitation of the analysis. Because repeated HRCT scans were not usually available, an anchor-based approach, that relies on the variability of anchored measurements, was selected in this study. Anchor-based methods require measurements of longitudinal change for the tool of interest and other anchor measurements that already have an established MCID. The estimates of MCIDs from other anchored measurements are likely overestimated because of the nature of additive variabilities. MCID estimates are approximations, and the recommended approach is to use multiple anchors to define a range of MCID estimates [37]. Both function and PROs are relevant when interpreting the outcomes of clinical trials. The MCIDs of the relationships between QLF and SGRQ (PRO) or FVC (lung function) in this study were less sensitive than the MCID of QLF using all-cause mortality as an anchor. The degree of QLF change needed to attain a meaningful, absolute change was 0.5-4.4% for SGRQ as an anchor, 2.0-4.3% for FVC as an anchor, and -1.6%-8.1% for concordance of SGRQ and FVC in non-stable change. This suggests that, for a meaningful change in PROs and function derived from Jaeschke's method, a greater amount of QLF change is needed in the evaluation of QLF with SGRQ or FVC than when using all-cause mortality as an anchor with multiple QLF thresholds. This reflects the progressive nature of IPF, which contrasts other chronic lung diseases, and the fact that the observations from the follow-up visits are based on stable or worsening disease. This is similar to findings by Kon et al., who reported that the MCID of an assessment tool for chronic obstructive pulmonary disease from a receiver operating characteristic (ROC) analysis was smaller than the MCID from an anchor-based approach [40]. Further, multivariable regression modelling, such as the anchor-based Jaeschke's method, that combine both clinical and subjective (e.g., PRO) parameters to quantify changes in the outcome

389	of interest (e.g., QLF) offer less-biased estimates of MCIDs than distribution-based methods,
390	which only assess the statistical significance of a change [41].
391	
392	The QLF changes of 1% and 2% at Week 24 presented in supplemental figures 3a and 3b ,
393	respectively, correspond to 25- and 46-mL changes. The structural changes are visualised both in
394	the right side (supplemental figure 3a) and left side of the lung (supplemental figure 3b).
395	These QLF changes are similar to the absolute mean changes of 2% and 56 mL (table 2) when
396	FVC was used as an anchor in our analysis. When retesting the MCID of the QLF score derived
397	from the MCID using SGRQ and ppFVC as anchors, the hazard ratio (HR) ranged from 4.33-
398	8.89, which is similar to the HRs of 4.98 and 4.04 for the relatively smaller MCIDs of 1% and
399	2%, respectively. The QLF scores associated with the MCIDs of SGRQ and ppFVC were greater
400	than the QLF score associated with survival, which suggests that these biomarkers require
401	greater structural disease progression before they can detect meaningful change. This also
402	suggests that QLF may be more sensitive than either ppFVC or SGRQ as a trial endpoint [42].
403	
404	There were 11 deaths in this study that occurred after Week 24. Because QLF changes were
405	derived from Week 24 and the screening HRCT scans, the median survivals were relatively
406	short. Week-48 data were omitted from the survival analysis because most changes in QLF were
407	observed within 24 weeks. In addition, including data beyond Week 24 had the potential to skew
408	the results by including patients with mild to moderate IPF who were more likely to remain alive
409	at 1 year. QLF change as a volume is a suitable clinical trial endpoint, as noted by the high HR in
410	table 4. Change in QLF extent can provide a normalised measurement regardless of the volume
411	differences between patients of different sex or height. Finally, the MCID of QLF is an early

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biomarker of change in lung fibrosis, so 48 weeks of data, which is often used for the primary
endpoints in IPF clinical trials, are not needed to determine the value of the MCID of the QLF
score and its clinical applicability for predicting early change.

> The multiple thresholds of QLF changes can be found in other studies. In an independent cohort of patients who received nintedanib (n=42) anti-fibrotic approved drug, mean absolute changes in QLF were 0.98% and a 21.7-mL increase at Month 6, and 1.4% and a 27.6-mL increase at Month 12. In the placebo arm of the same trial, the changes were 1.33% and 37.3mL at Month 6 and 2.2% and 67.0mL at Month 12. Negative correlations were observed between change in QLF score and change in FVC at Month 6, supporting the findings of the QLF score [21]. In a retrospective analysis of approximately 200 patients with IPF, 4% change in QLF score for the most severe lobe and for the whole lung at 6 months was associated with a three- to five-fold increased risk of clinical progression [43]. Further, a placebo-controlled Phase II trial of 137 patients with IPF reported significant correlations between OLF and ppFVC changes, as well as other symptoms of IPF, where the most of subjects in the placebo arm were within $\pm 2\%$ changes at week 24 [25]. Overall, QLF measured on HRCT, where the most of 6 month mean changes range from 1-4%, has proven to be useful as an efficacy endpoint in clinical trial settings.

This study has several limitations. First, it was a *post hoc* rather than an *a priori* analysis of data
from two Phase II clinical trials. Thus, due to the nature of Phase II studies, mortality was based
on a short follow-up period. In addition, allocation of treatment arms and study locations were
different between the studies. Specifically, Study 049 was a single-arm study, whereas Study 067
was a randomised study with one-to-one allocation of placebo and pamrevlumab. Further, Study

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049 took place only in the United States, and Study 067 involved patients worldwide. Sub-cohorts of patients who received pamrevlumab or other treatments were not analysed separately here for purposes of simplification. Additionally, this study analysed the usefulness of QLF change for predicting mortality risk only over a short period of time. Second, we used MCID derived from a distribution-based approach for ppFVC and the symmetric changes in ± 5 points SGRQ, which is close to 4.9 changes reported by Prior et al for deterioration, where most IPF subjects feel worsening or stable in their symptoms. We used ± 5 where the subject-level changes of SGRQ is an integer change, and MCID of SGRQ considered to be around 4-5 points [32, 45, 46]. Third, we did not estimate MCID using a distribution-based approach because the extra radiation exposure required for patients to estimate the MCID was not well-justified. Fourth, a single quantitative HRCT score for IPF was applied. The estimated MCID may not be generalizable to other available quantitative scores. Fifth, caution should be applied when applying the estimated MCID for the observational or registry studies, in which HRCT scans are not performed routinely. In this study, HRCT scans were scheduled and performed as part of clinical trials. Lastly, phase III studies did not show efficacy of pamrevlumab [11-13], this study used survival as the primary endpoint to assess MCID.

We believe our analyses begin the evidence-generation process of using multiple thresholds for validation of a biomarker [44]. The MCID of QLF in IPF has demonstrated clinical validity. The estimated MCID of 2% may be considered for associating changes in mortality, lung function, and patient symptoms in ongoing and future trials of IPF, where the metric can be normalised to the volume of QLF changes for both sexes. The greater MCID of QLF using the MCID of SGRQ and ppFVC may suggest that structural changes precede functional changes. The change of QLF

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2 3 4	458	volume is a sensitive measurement that can be considered in applying an imaging outcome as a
- 5 6	459	potential efficacy endpoint when the extent of structural fibrosis is assessed via HRCT.
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471	contributed the acquisition of the work. XZ contributed the analysis of the data. All authors
472	contributed to the interpretation of the data for the work the drafting the work or review critically
473	for the important intellectual content and development of the manuscript and reviewed and
474	approved the final manuscript for submission. And all the authors agreed to be accountable for
475	all aspects of the work in ensuring that questions related to the accuracy or integrity of any part
476	of the work are appropriately investigated and resolved. GJK is responsible for the overall
477	content as guarantor.
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482	Competing interests LP was a former employee of FibroGen, Inc., at the time of the study, but
483	is now an employee of and holds stock options in Pliant Therapeutics Inc. XZ was a former
484	employee of FibroGen Inc. at the time of the study but is now an employee of and holds stock
181	ontions in Neumora Therapeutics. Inc. IGG and MSB are former founders of MedOIA and hoard
LOL	options in recumora rinerapeuties, me. 300 and wish are former founders of wedgite and board
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members of Voiant. GJK is a former consultant to MedOIA and current consultant to Voiant. 486 GJK, MSB, and JGG are a patent developer of the issued patent: UC-2013-078-2-LA-EP. 487 **Patient and public involvement** No patients or members of the public were involved in the 488 design, conduct, reporting, or dissemination plans of this study. 489 **Patient consent for publication** Consent obtained directly from patient(s). 490 491 **Provenance and peer review** Not commissioned; externally peer reviewed. Data availability statement FibroGen, Inc., is committed to data sharing and to furthering 492 medical research and patient care. Based on scientific merit, requests from qualified external 493 494 researchers for anonymised patient-level and study-level clinical trial data (including redacted clinical study reports) for medicines and indications approved in the United States and Europe 495 will be considered after the respective primary study is accepted for publication. All data 496 provided are anonymised to respect the privacy of patients who have participated in the trial in 497 line with applicable laws and regulations. 498 Supplemental material This content has been supplied by the author(s). It has not been vetted 499 by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions 500 or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. 501 BMJ disclaims all liability and responsibility arising from any reliance placed on the content. 502 Where the content includes any translated material, BMJ does not warrant the accuracy and 503 504 reliability of the translations (including but not limited to local regulations, clinical guidelines, 505 terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise. 506 507 **Open access** 508 **ORCID iD**

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44 45	663	FIGU	RE	
46 47	664	Figure	e 1. Use of HRCT to calculate QLF. QLF is a specific method (UCLA patent) that utilises	3
48 49 50	665	image	normalization (denoising) to minimise cross-site variability within images, resulting in	
50 51 52	666	decom	posed CT images prior to texture calculation.	
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3 4	668	Footnote: CT, computed tomography; HRCT, high-resolution computed tomography; LF, lung
5 6	669	fibrosis; QLF, quantitative lung fibrosis; UCLA, University of California at Los Angeles
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Figure 1. Use of HRCT to calculate QLF. QLF is a specific method (UCLA patent) that utilises image normalization (denoising) to minimise cross-site variability within images, resulting in decomposed CT images prior to texture calculation. /CT, computed tomography; HRCT, high-resolution computed tomography; LF, lung fibrosis; QLF, quantitative lung fibrosis; UCLA, University of California at Los Angeles.

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BMJ Open **Supplemental figure 3 (a).** QLF patterns in a 75-year-old female patient with IPF: (A) coronal HRCT integers; (B) axial HRCT images. QLF changes were 1% and 25.32 mL at Week 24. QLF score annotated by blue and red dots. The changes of 1% and ≥ 20 mL represent the minimum sensitivity requirements. Whole lung volume was 3414 mL at baseline and 3316 HL & Week 24 in the



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Variable	Category	Combined group (Study 049 + Study 067) (N=190)	Study 049 (n=89)	Study 067 (n=101)
Age, y	Median (range)	68 (46-82)	68 (47–82)	68 (46-80)
Weight, kg			89.1 (56.8–	
	Median (range)	86.3 (46–127.6)	121.8)	82.7 (46–127.6)
Time since first				
IPF diagnosis, y	Median (range)	1.1 (0–6.0)	1.5 (0.1–6.0)	0.9 (0.0-4.9)
Lung function				
FVC, L	Median (range)	2.62 (1.28-5.51)	2.53 (1.32–5.51)	2.78 (1.28-4.45)
FVC, %	Median (range)	69.5 (42.6–	65.9 (42.6–	71.8 (53.9–
predicted		111.7)	111.7)	102.1)
DLCO, % predicted	Median (range)	49.8 (28.2–94.5)	47.4 (30.4–94.5)	53.6 (28.2–85.9)
FEV ₁ /FVC ratio	Median (range)	0.82 (0.65-0.95)	0.83 (0.65-0.94)	0.81 (0.66-0.95)
HRCT ^a				
Whole lung	Median (range)	3.91 (1.52-6.49)	3.57 (2.40-6.49)	4.09 (1.52-6.33)
volume, L				
QLF, %	Median (range)	15 (2–52)	18 (2–51)	13 (2–52)
QLF, mL	Median (range)	559.65 (66.02-	619.31 (66.02–	494.94 (86.18–
		2325.50)	2325.50)	1603.94)
GAP ^b				
GAP score	Median (range)	4 (0-7)	4 (1–7)	4 (0-6)

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		BMJ Open				
Symptom						
Score						
SGRQ	Median (range)	42.5 (0.8-86.4)	45.6 (11.3-81.4)	40.3 (0.8-86.4)		
LICSD_SOBO	Median (range)	30.0(1.0-85.0)	30.0 (2.1-85.0)	310(10-830)		

DLCO, diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in 1 second; FVC, forced main a capacity; GAP, DLCO, diffusing capacity for carbon monoxide, FDV1, forect explanately gender, age, physiology; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosts DLF, quantitative lung fibrosis; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; UCSD-SOBQ, University California San Diego, Shortness of Breath Questionnaire. ^aComputer-assisted QLF scores were derived from volumetric scans of the whole lung. ^b Gender-Age-Pulmonary (GAP) function score. La tomograp. Respiratory Quesi. rom volumetric scans of the white score.
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	Cha	nges in QLF score (%),
		mean (SD)	
	Week 2	24	
		SGRQ stable	SGRQ worsened
	SGRQ improved	(-5 to 5),	(≥5),
	(≤-5), n=48	n=63	n=41
ppFVC improved	n=5	n=11	n=4
(≥3.4%), n=20	-1.6 (3.71)	-1.3 (3.98)	0.5 (0.58)
ppFVC stable	n=31	n=36	n=17
(-3.4% to 3.4%),	0.9 (2.94)	0.5 (3.75)	2.1 (3.04)
n=84			
ppFVC worsened	n=12	n=16	n=20
(≤-3.4%), n=48	2.3 (2.42)	1.7 (3.32)	8.1 (8.27)
	Week 4	18	

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		SGRQ stable	SGRQ worsened
	SGRQ improved	(-5 to 5),	(≥5),
	(≤-5), n=40	n=54	n=39
ppFVC improved	n=5	n=11	n=3
(≥3.4%), n=19	-3.4 (6.50)	0.6 (2.11)	0.7 (1.53)
ppFVC stable	n=24	n=23	n=15
(-3.4% to 3.4%),	0.3 (3.65)	2.5 (4.31)	1.9 (4.09)
n=62			
ppFVC worsened	n=11	n=20	n=21
(≤-3.4%), n=52	1.9 (3.27)	5.5 (5.90)	7.9 (7.37)

 ppFVC, percent-predicted forced vital capacity; QLF, quantitative lung fibrosis; SD, standard deviation; SG, St. George's Respiratory Questionnaire.

Note: mean QLF changes when patients experienced discordance of symptoms were calculated as follow For worsening of one parameter, mean QLF change at Week $24 = (4 \times 0.5\% + 17 \times 2.1\% + 12 \times 2.3\% + 16 \times 1.7\%)/(4 + 17 + 12 + 16) = 1.8\%$ For mean QLF change at Week $48 = (3 \times 0.7\% + 15 \times 1.9\% + 11 \times 1.9\% + 20 \times 5.5\%)/(3 + 15 + 11 + 20) = 3.3\%$. For improvement of one parameter, mean QLF change at Week $24 = (11 \times -1.3\% + 4 \times 0.5\% + 31 \times 0.9\% + 12 \times 2.3\%)/(11 + 4 + 31 + 12) = 0.7\%$; mean QLF change at Week $28 = (11 \times 0.6\% + 3 \times 0.7\% + 24 \times 0.3\% + 11 \times 1.9\%)/(11 + 3 + 24 + 11) = 0.8\%$.

Note: The discordant changes when one parameter worsened were associated with the mean QLF changes of pproximately 2%; discordant changes with one parameter improved were associated with QLF changes of approximately within $\pm 1\%$,

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 BMJ Open BMJ Open Supplemental table 3. Relationship of QLF as a percentage and a volume with MCID of SGRQ and pperformed by Copyright, inclusion of the second sec

							Weels 24				<u>c</u>		<u>.</u>								
	1			SCDO			Week 24														
						Unadjusted analysis		Unadjusted analysis		Adjusted analysis, mean (95% CI)	Unadju analys	sted sis	Adjusted analysis, mean (95% CI)		Unadjı analy	ısted 7sis	Adjusted analysis, mean	nseignemen	y Unadjus analys	sted is	Adjusted analysis, mean (95% CD
	N	QLF change, % mean (95% CI)	ES	QLF change, % mean (95% CI)	QLF change, mL mean (95% CI)	ES	QLF change, mL mean (95% CI)	Ν	QLF change, % mean (95% CI)	ES	QLF change, % mean (95% CI)a	Willogued Ingit	QLF hange, mL mean \$% CI)	ES	QLF change, mL mean (95% CI)						
Combined g	group /											<u>s</u> S	5		1						
Worsened ^a	41	4.88 (3.46, 6.30)	1.08	4.39 (2.97, 5.81)	111.94 (77.60, 146.28)	1.03	90.81 (56.47, 125.15)	49	4.55 (3.27, 5.83)	1.02	3.56 (2.28, 2 4.84)		01.90 70.30, 33.49)	0.93	64.67 (33.07, 96.26)						
Stable ^a	63	0.49 (-0.66, 1.64)	0.11	0 (-1.15, 1.15)	21.13 (-6.58, 48.83)	0.19	0 (-27.71, 27.70)	86	0.99 (0.02, 1.96)	0.22	0 ب (–0.97, و 0.97)	Sumo or	37.23 13.38, 51.08)	0.33	0.00 (-23.85, 23.85)						
Improved ^a	48	$ \begin{array}{r} 1.00 \\ (-0.32, \\ 2.32) \end{array} $	0.22	0.51 (-0.81, 1.83)	31.27 (-0.47, 63.01)	0.29	10.14 (-21.60, 41.88)	20	$ \begin{array}{c} -1.00 \\ (-3.01, \\ 1.01) \end{array} $	-0.23	-1.99 (-4.00, 0.02)		18.46 67.92, 0.99)	0.17	-55.69 (-105.15, -6.24)						
Study 049													5								
Worsened ^a	22	6.59 (4.16, 9.02)	1.21	6.38 (3.95, 8.81)	137.19 (82.92, 191.45)	1.12	124.14 (69.87, 178.40)	22	6.50 (4.12, 8.88)	1.21	5.23 (2.85, 7.61)		29.62 76.20, 83.05)	1.08	91.92 (38.50, 145.35)						
Stable ^a	29	0.21 (-1.91, 2.32)	0.04	0 (-2.12, 2.11)	13.05 (-34.22, 60.31)	0.11	0 (-47.27, 47.26)	44	1.27 (-0.41, 2.95)	0.23	0 (-1.68, 1.68)	o ar a nac	37.70 -0.08, 5.48)	0.30	0.00 (-37.78, 37.78)						
Improved ^a	22	1.27 (-1.15, 3.70)	0.23	1.06 (-1.36, 3.49)	30.96 (-23.30, 85.23)	0.25	-17.91 (-36.65, 72.18)	8	-2.63 (-6.56, 1.31)	-0.56	-3.90 (-7.83, 0.04)		59.52 448.12, 9.08)	0.56	-97.22 (-185.82, 8.62)						
Study 067			•							•		, G									
Worsened ^a	19	2.89	0.98	2.15	82.71	0.93	54.69	27	2.96	1.00	2.27	4	79.30	0.85	42.56						
									(-h		-la face l	indre de i			9						

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		(1.47,		(0.73,	(39.77,		(11.75,		(1.79,		(1.10,	2 .23,		(5.49,				
Q4 - 1- 1 - 9	24	4.32)	0.24	3.58)	125.65)	0.20	97.63)	42	4.14)	0.22	<u>3.45) 6</u>	(0.38)	0.20	79.76)				
Stable	34	0.74	0.24		28.02	0.30		42	0.69	0.23		97 01	0.39					
		(-0.33, 1.80)		(-1.07, 1.06)	(-4.08, 60.12)		(-32.10, 32.10)		(-0.23, 1.63)		$(-0.94, \mathbf{G})$	6 46)		(-29.73)				
Improveda	26	0.77	0.25	0.03	31.53	0.35	3 51	12	0.08	0.03		<u></u>	0.10	_27.73				
Impioved	20	(-0.45)	0.25	(-1.19	(-5.18)	0.55	(-33.2)	12	(-1.68	0.05	(-2.37)	E (S 46 70	0.10	(-83.44)				
		1 99)		1 25)	68 24)		40.22)		1 84)		115	ng 40.70,		27 78				
		1.57)	1	1.20)	00.21)		Week 48	8 29 0										
				SGRO)						FV@							
		Unadjus analys	sted is	Adjusted analysis, mean	Unadjusted analysis		Adjusted analysis, mean	d 5,	Unadjusted analysis		Adjustedo analysis, o mean	n D OUnadjusted out of analysis on one of the second secon		Adjusted analysis, mean				
		N	N	N	N		EC	(95% CI)	OLE	EC	(95% CI)	N	OLE	EC	(95% CI)		EC	(95% C
	N	QLF	ES		QLF	ES	QLF		QLF	ES	QLF dat		ES	QLF				
		change,		change,	mI	\mathbf{O}	mI				change, a	D _mI		mI				
		70 maan		70 maan	maan		maan		70 maan					maan				
		(05% CI)			(050/				incan (050)									
					195%				195%	1		·/\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		1977/01				
		(3370 CI)		(95% CI)	(95%) CD		(95% CI)		(95%) CD		(95% CI) <u>P</u> >	·(%% CI)		(95% C				
Combined g	roup	(9370 CI)		(95% CI)	(95%) CI)		(95% CI)		(95%) CI)		(95% Cip <u>Þ</u>	·(%3% CI)		(95% C				
Combined g Worsened ^a	roup 42	5.52	1.01	(95% CI) 2.30	(95%) CI) 157.32	1.17	(95% CI) 80.75	53	(95% CI) 5.75	1.14		•(%3% CI) 9 355.99	1.18	107.61				
Combined g Worsened ^a	roup 42	5.52 (3.82,	1.01	2.30 (0.60,	(95% CI) 157.32 (115.54,	1.17	80.75 (38.97,	53	(95% CI) 5.75 (4.37,	1.14	4.27 m (2.89, m	•(95% CI) • • • • • • • • • • • • •	1.18	107.61 (71.14				
Combined g Worsened ^a	roup 42	5.52 (3.82, 7.23)	1.01	2.30 (0.60, 4.01)	(95% CI) 157.32 (115.54, 199.10)	1.17	80.75 (38.97, 122.53)	53	(95% CI) 5.75 (4.37, 7.14)	1.14	(95% Clig 4.27 min (2.89, ng 5.66) a	•(5 % CI) 5 5 5 5 5 5 5 5	1.18	(93% C 107.61 (71.14 144.07				
Combined g Worsened ^a Stable ^a	roup 42 54	5.52 (3.82, 7.23) 3.22	1.01	2.30 (0.60, 4.01) 0	(95% CI) 157.32 (115.54, 199.10) 76.57	1.17	80.75 (38.97, 122.53) 0	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48	0.29	(95% C1)2 4.27 ming (2.89, gg 5.66) and 0.00 dd	•(43% C1) • • • • • • • • • • • • •	0.36	107.61 (71.14 144.07 0.00				
Combined g Worsened ^a Stable ^a	roup 42 54	5.52 (3.82, 7.23) 3.22 (1.72,	1.01 0.58	2.30 (0.60, 4.01) 0 (-1.50,	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72,	0.57	80.75 (38.97, 122.53) 0 (-36.85,	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20,	0.29	(95% C1)2 2 4.27 min (2.89, gg 5.66) an 0.00 dd (-1.28, sig	55.99 55.99 19.52 , 19.45 48.38 44.67 ,	1.18 0.36	107.61 (71.14 144.07 0.00 (-33.71				
Combined g Worsened ^a Stable ^a	roup 42 54	5.52 (3.82, 7.23) 3.22 (1.72, 4.73)	1.01 0.58	2.30 (0.60, 4.01) 0 (-1.50, 1.51)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42)	0.57	80.75 (38.97, 122.53) 0 (-36.85, 36.85)	53 62	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76)	0.29	(95% C1)2 2 4.27 (2.89, g, 5.66) and 0.00 d (-1.28, similar 1.28) list	•(4 % C1) • 6 • 5 • 7 • 7	1.18 0.36	107.61 (71.14 144.07 0.00 (-33.71 33.71)				
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39	1.01 0.58 0.07	2.30 (0.60, 4.01) 0 (-1.50, 1.51) -2.83	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14	1.17 0.57 0.17	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65	1.14 0.29 -0.14	(95% C1)2 2 4.27 (2.89, g, 5.66) an 0.00 (-1.28, similar 1.28) -2.13	•(1% C1) • 9 • 1 55.99 • 1 9.52, • 1 92.45) • 1 4.67, • 2 2.09) • 1 16.46	1.18 0.36	107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84				
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34,	1.01 0.58 0.07	$\begin{array}{c} 2.30 \\ (0.60, \\ 4.01) \\ 0 \\ (-1.50, \\ 1.51) \\ -2.83 \\ (-4.56, \end{array}$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15,	1.17 0.57 0.17	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72,	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90,	1.14 0.29 -0.14	(95% Clip 4.27 ining (2.89, g, 5.66) and (-1.28, imin 1.28) inin -2.13 r tech (-4.38, ecr	•(19% C1) • (19% C1) • (19,52, • (19,52,	1.18 0.36 - 0.13	107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1				
Combined g Worsened ^a Stable ^a Improved ^a	roup 42 54 41	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12)	1.01 0.58 0.07	$\begin{array}{c} 2.30 \\ (0.60, \\ 4.01) \\ 0 \\ (-1.50, \\ 1.51) \\ -2.83 \\ (-4.56, \\ -1.10) \end{array}$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42)	1.17 0.57 0.17	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15)	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60)	1.14 0.29 -0.14	(95% C1)2 ≥ 4.27 (2.89, g, 5.66) and (-1.28, mil 1.28) ar (-4.38, cc 0.12) m	•(************************************	1.18 0.36 - 0.13	107.61 (71.14 144.07 0.00 (-33.71) -64.84 (-124.1 -5.48)				
Combined g Worsened ^a Stable ^a Improved ^a Study 049	roup 42 54 41	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12)	1.01 0.58 0.07	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42)	1.17 0.57 0.17	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15)	53 62 20	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60)	1.14 0.29 0.14	(95% C1)2 2 4.27 (2.89, g, 5.66) and (-1.28, and (-1.28, and (-4.38, chnological of the second secon	•(13% C1) • • • • • • • • • • • • •	1.18 0.36 0.13	(93% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48)				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a	roup 42 54 41 23	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83	1.01 0.58 0.07 0.91	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85	1.17 0.57 0.17 1.03	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98	53 62 20 33	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70	1.14 0.29 -0.14 1.24	(95% C1)2 A 4.27 (2.89, g, 5.66) and (-1.28, and (-1.28, and (-1.28) art tech (-4.38, chn 0.12) art tech 0.12) art t	•(13% C1) • (19,52, • (19,52,	1.18 0.36 - 0.13 1.18	(93% C 107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48) 169.32				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a	roup 42 54 41 23	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, (3.06,	1.01 0.58 0.07 0.91	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11,	1.17 0.57 0.17 1.03	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 12.76, 12.76)	53 62 20 33	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78,	1.14 0.29 -0.14 1.24	(95% C1)2 2 4.27 (2.89, g, 5.66) and (-1.28, similar (-4.38, cc, 0.12) of 5.97 ies (4.05, s.	•(1) •(1)	1.18 0.36 	$\begin{array}{c} 107.61\\ (71.14\\ 144.07\\ 0.00\\ (-33.71\\ 33.71)\\ -64.84\\ (-124.1\\ -5.48)\\ 169.32\\ (114.6)\\ \end{array}$				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a	roup 42 54 41 23	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59)	1.01 0.58 0.07 0.91	(95% C1) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$ $3.78)$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60)	1.17 0.57 0.17 1.03	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73)	53 62 20 33	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62)	1.14 0.29 -0.14 1.24	(95% C1)2 4.27 ming 5.66) and (-1.28, and (-1.28, and (-1.28, and (-4.38, control of the second secon	•(1) •(1)	1.18 0.36 - 0.13 1.18	107.61 (71.14 144.07 0.00 (-33.71 33.71) -64.84 (-124.1 -5.48) 169.32 (114.61 224.03				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$ $3.78)$ 0 $(-1.75,$ $(-1.75,$ $-1.75,$ $(-$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (19.5)	1.17 0.57 0.17 1.03 0.67	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (0, 128.73)	53 62 20 33 22	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (1.5)	1.14 0.29 -0.14 1.24 0.14	(95% C1)2 4.27 ining 5.66) and (-1.28, ining 1.28) ining (-4.38, control (-4.38, control	•(1) •(1)	1.18 0.36 - 0.13 1.18 0.08	$\begin{array}{c} 107.61\\ (71.14\\ 144.07\\ 0.00\\ (-33.71\\ 33.71)\\ -64.84\\ (-124.1\\ -5.48)\\ 169.32\\ (114.61\\ 224.03\\ 0.00\\ 0.00\\ \end{array}$				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81 (2.21,	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 $(0.60, 4.01)$ 0 $(-1.50, 1.51)$ -2.83 $(-4.56, -1.10)$ 1.02 $(-1.75, 3.78)$ 0 $(-2.60, 0)$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41)	1.17 0.57 0.17 1.03 0.67	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 6.54)	53 62 20 33 22	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 2.62)	1.14 0.29 -0.14 1.24 0.14	(95% C1)2 4.27 min (2.89, g 5.66) and (-1.28, mil (-4.38, c 0.12) old 5.97 (4.05, 7.89) 0.00 (-2.35, 0.00) (-2.35, 0.00)	•(13% C1) •(19,52, •(19,	1.18 0.36 - 0.13 1.18 0.08	107.61 (71.14 144.07 0.00 (-33.71) -64.84 (-124.1) -5.48) 169.32 (114.61 224.03 0.00 (-67.01				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a	roup 42 54 41 23 26	5.52 (3.82, 7.23) 3.22 (1.72, 4.73) 0.39 (-1.34, 2.12) 5.83 (3.06, 8.59) 4.81 (2.21, 7.41)	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$ $3.78)$ 0 $(-2.60,$ $2.60)$ 5.10	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41)	1.17 0.57 0.17 1.03 0.67	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54)	53 62 20 33 22 11	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08)	1.14 0.29 -0.14 1.24 0.14	(95% C1g 2 4.27 (2.89, g, 5.66) an 0.00 d (-1.28, similar (-4.38, chn 0.12) o 5.97 (4.05, s. 7.89) 0.00 (-2.35, 2.35)	•(1) •(1)	1.18 0.36 - 0.13 1.18 0.08	$\begin{array}{c} \textbf{(93\% C)}\\ \textbf{(93\% C)}\\ \textbf{(107.61)}\\ \textbf{(71.14)}\\ \textbf{(144.07)}\\ \textbf{0.00}\\ \textbf{(-33.71)}\\ \textbf{-64.84}\\ \textbf{(-124.11)}\\ \textbf{-64.84}\\ \textbf{(-124.11)}\\ \textbf{-5.48)}\\ \textbf{169.32}\\ \textbf{(114.61)}\\ \textbf{224.03}\\ \textbf{0.00}\\ \textbf{(-67.01)}\\ \textbf{0.00}\\ \textbf{(-67.01)}\\ \textbf{67.00)} \end{array}$				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a Improved ^a	roup 42 54 54 41 23 26 17	(5376 CI) 5.52 $(3.82, 7.23)$ 3.22 $(1.72, 4.73)$ 0.39 $(-1.34, 2.12)$ 5.83 $(3.06, 8.59)$ 4.81 $(2.21, 7.41)$ -0.59	1.01 0.58 0.07 0.91 0.75	(95% CI) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$ $3.78)$ 0 $(-2.60,$ $2.60)$ -5.40 (-5.40)	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41) -20.49	1.17 0.57 0.17 1.03 0.67	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54) -130.36	53 62 20 33 22 11	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08) -1.73	1.14 0.29 -0.14 1.24 0.14 -0.35	(95% C1g 2 4.27 (2.89, g, 5.66) an 0.00 d (-1.28, sin 1.28) 11 (-4.38, con 0.12) 00 5.97 (4.05, s. 7.89) 0.00 (-2.35, 2.35) -2.46	•(1) •(1)	1.18 0.36 	$\begin{array}{c} 107.61\\ (71.14\\ 144.07\\ 0.00\\ (-33.71\\ 33.71)\\ -64.84\\ (-124.1\\ -5.48)\\ 169.32\\ (114.61\\ 224.03\\ 0.00\\ (-67.01\\ 67.00)\\ -62.90\\ \end{array}$				
Combined g Worsened ^a Stable ^a Improved ^a Study 049 Worsened ^a Stable ^a Improved ^a	roup 42 54 54 41 23 26 17	(5376 CI) 5.52 $(3.82, 7.23)$ 3.22 $(1.72, 4.73)$ 0.39 $(-1.34, 2.12)$ 5.83 $(3.06, 8.59)$ 4.81 $(2.21, 7.41)$ -0.59 $(-3.80, 20)$	1.01 0.58 0.07 0.91 0.75 - 0.09	(95% C1) 2.30 $(0.60,$ $4.01)$ 0 $(-1.50,$ $1.51)$ -2.83 $(-4.56,$ $-1.10)$ 1.02 $(-1.75,$ $3.78)$ 0 $(-2.60,$ $2.60)$ -5.40 $(-8.61,$ $-1.0)$	(95% CI) 157.32 (115.54, 199.10) 76.57 (39.72, 113.42) 22.14 (-20.15, 64.42) 167.85 (97.11, 238.60) 109.87 (43.33, 176.41) -20.49	1.17 0.57 0.17 1.03 0.67 0.13	80.75 (38.97, 122.53) 0 (-36.85, 36.85) -54.53 (-96.72, -12.15) 57.98 (-12.76, 128.73) 0 (-66.54, 66.54) -130.36 (-212.65, 40.57)	53 62 20 33 22 11	(95% CI) 5.75 (4.37, 7.14) 1.48 (0.20, 2.76) -0.65 (-2.90, 1.60) 6.70 (4.78, 8.62) 0.73 (-1.62, 3.08) -1.73 (-5.05,	1.14 0.29 -0.14 1.24 0.14 -0.35	(95% C1)2 24.27 (2.89, g, 5.66) an 0.00 (-1.28, similar (-4.38, constant (-4.38, constant (-2.35, 2.35) (-2.46 (-5.78, constant (-5.78, constant	•(1) •(1)	1.18 0.36 0.13 1.18 0.08 0.36	$\begin{array}{c} 107.61\\ (71.14\\ 144.07\\ 0.00\\ (-33.71\\ 33.71)\\ -64.84\\ (-124.1'\\ -5.48)\\ \hline 169.32\\ (114.61\\ 224.03\\ 0.00\\ (-67.01\\ 67.00)\\ -62.90\\ (-157.66\\ -157.66\\$				

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3						(-							24-(t, i		
4						102.78,							094		
5						61.80)							155 ud		
6	Study 067												ing		
7	Worsened ^a	19	5.16	1.26	3.41	144.57	1.65	98.92	20	4.20	0.96	2.30	T T 13.39	1.16	45.26
8			(3.18,		(1.43,	(102.25,		(56.6,		(2.16,		(0.26,	č 6 7.81,		(-0.32,
9			7.14)		5.39)	186.90)		141.25)		6.24)		4.34)			90.84)
10	Stable ^a	28	1.75	0.42	0	45.65	0.51	0	40	1.90	0.42	0.00	S S S 8.13	0.68	0.00
11			(0.12,		(-1.63,	(10.78,		(-34.87,		(0.46,		(-1.44,	a 5.90,		(-32.23,
12			3.38)		1.63)	80.51)		34.86)		3.34)		1.44)	g <u>s</u> <u>10</u>0.36)		32.23)
13	Improved ^a	24	1.08	0.26	-0.67	52.33	0.59	6.68	9	0.67	0.17	-1.23	to 9 025.06	0.28	-43.07
14	_		(-0.68,		(-2.43,	(14.67,		(-30.98,		(-2.38,		(-4.28,	ຄັບອີ42.90,		(-111.03,
15			2.85)		1.10)	89.99)		44.34)		3.71)		1.81)	ਸ ਦ ਹ 3.01)		24.88)

Note: Negative sign denotes decline in ppFVC. predicted forced vital capacity; QLF, quantitative lung fibrosis; SGRQ, St. George's Respiratory Question 2012 ^aWorsened: SGRQ change ≥ 5 points or ppFVC change $\leq -3.4\%$; stable: SGRQ change between -5 and 5 boints or ppFVC change between -3.4% and 3.4%; improved: SGRQ change ≤ -5 points or ppFVC change $\geq 3.4\%$.

Al training, and similar technologies mjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de

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