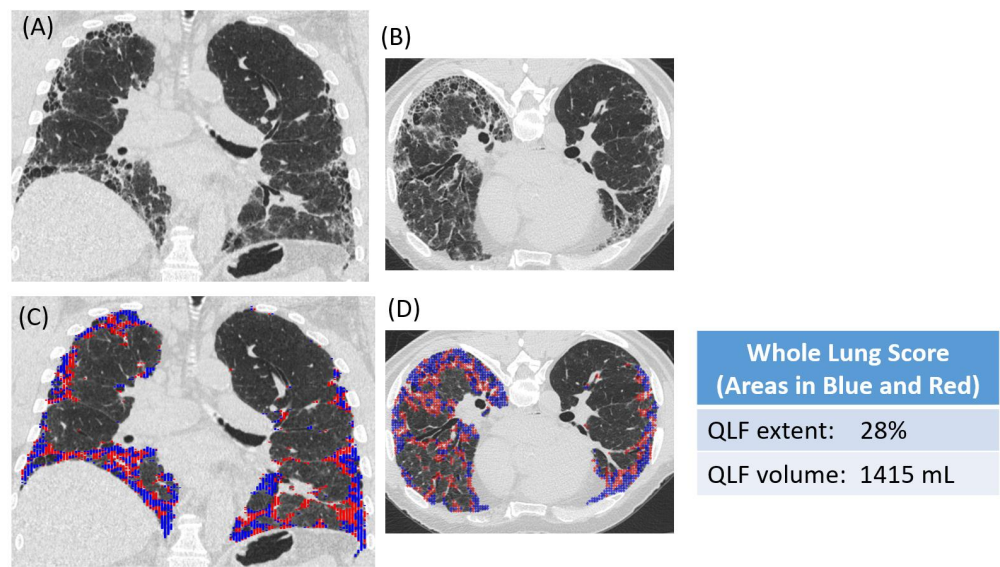
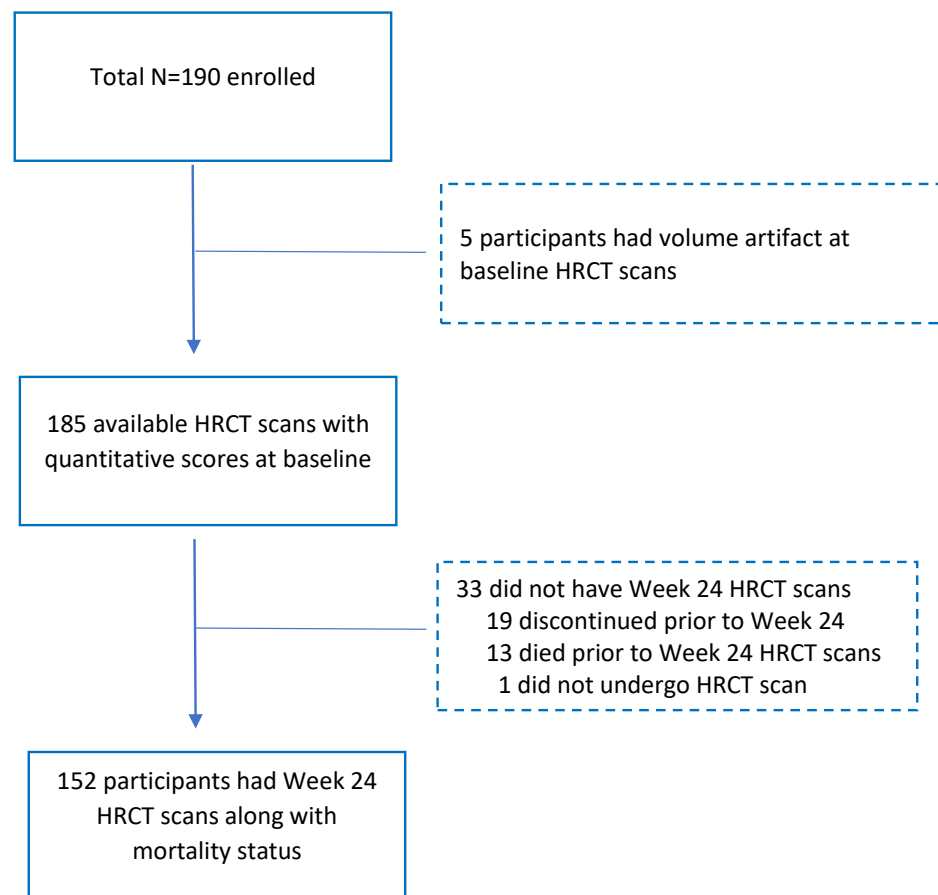


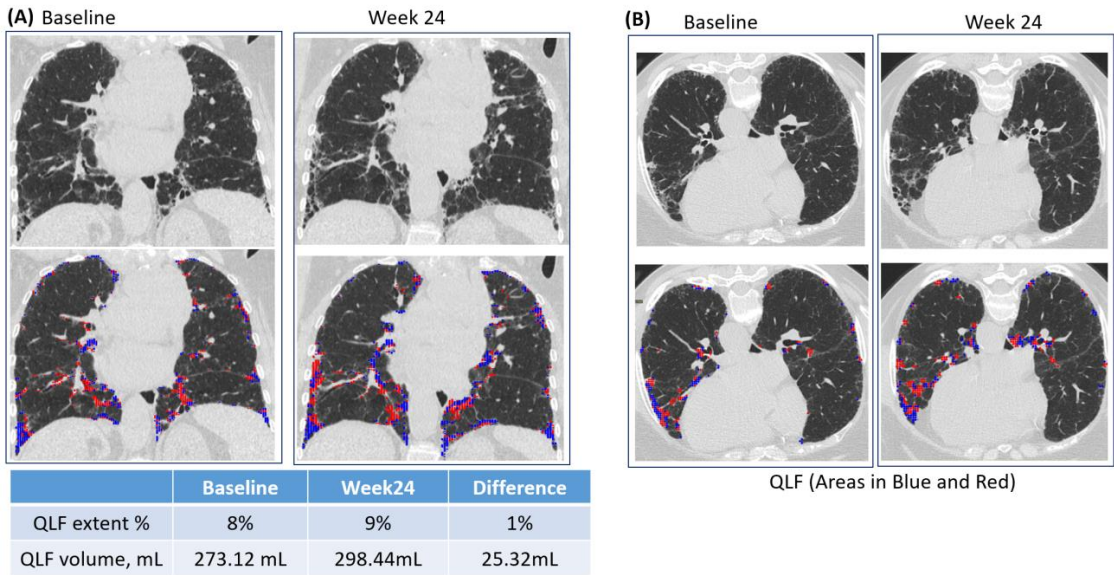
Supplemental figure 1. QLF patterns in a patient with IPF: (A) coronal chest HRCT, (B) axial HRCT, (C) overlaid QLF classification result of (A) annotated by blue and red dots, (D) overlaid QLF classification result of (B). Total QLF changes of 28% and 1415 mL in the whole lung were determined using the physical measurement of voxel size (basic unit of HRCT image).



HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; QLF, quantitative lung fibrosis.

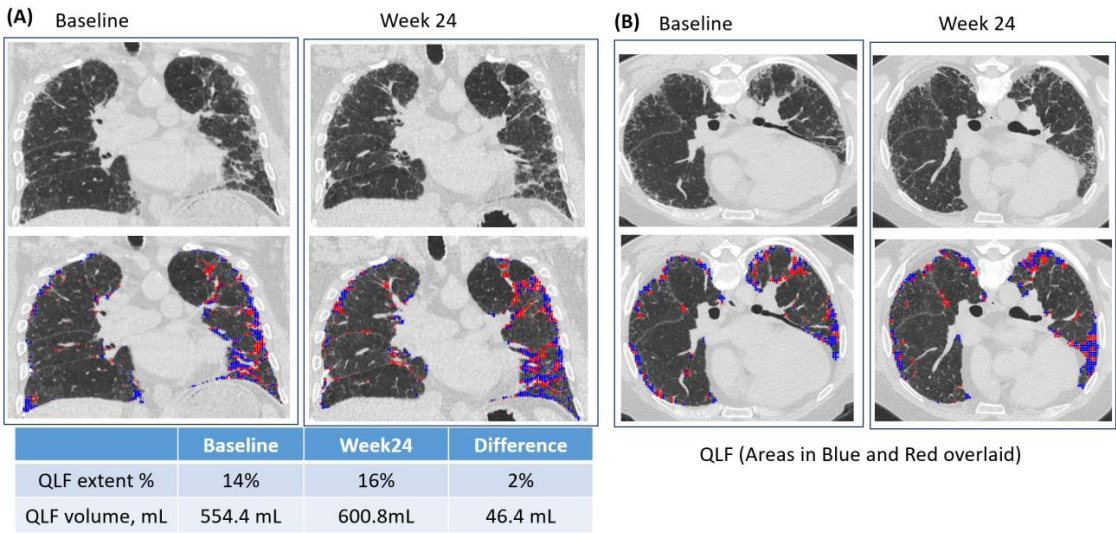
Supplemental figure 2. Flow of participants

Supplemental figure 3 (a). QLF patterns in a 75-year-old female patient with IPF: (A) coronal HRCT images; (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 mL at Week 24 in the inspirational HRCT scans.



HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; QLF, quantitative lung fibrosis.

Supplemental figure 3 (b). QLF patterns in a 63-year-old male with IPF: (A) coronal HRCT images; (B) axial HRCT images. QLF changes were 2% and 46.4 mL at Week 24. QLF score annotated by blue and red dots. The changes of 2% and ≥ 40 mL met the minimum sensitivity requirements. Whole lung volume was 3960 mL at baseline and 3755 mL at Week 24 in the inspirational HRCT scans.



Supplemental table 1. Demographics and baseline clinical characteristics using median and range

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, % predicted	Median (range)	69.5 (42.6– 111.7)	65.9 (42.6– 111.7)	71.8 (53.9– 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 volume, L	Median (range)	3.91 (1.52–6.49)	3.57 (2.40–6.49)	4.09 (1.52–6.33)
QLF, %	Median (range)	15 (2–52)	18 (2–51)	13 (2–52)
QLF, mL	Median (range)	559.65 (66.02– 2325.50)	619.31 (66.02– 2325.50)	494.94 (86.18– 1603.94)
GAP ^b				
GAP score	Median (range)	4 (0–7)	4 (1–7)	4 (0–6)
Symptom				

Score				
SGRQ	Median (range)	42.5 (0.8–86.4)	45.6 (11.3–81.4)	40.3 (0.8–86.4)
UCSD-SOBQ	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; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GAP, gender, age, physiology; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; QLF, quantitative lung fibrosis; SD, standard deviation; SGRQ, St. George’s Respiratory Questionnaire; UCSD-SOBQ, University of California San Diego, Shortness of Breath Questionnaire.

^aComputer-assisted QLF scores were derived from volumetric scans of the whole lung.

^bGender-Age-Pulmonary (GAP) function score.

Supplemental table 2. Changes in QLF scores (%) at Weeks 24 and 48 by changes in SGRQ and ppFVC

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

	(≤ -5), n=40	(-5 to 5), n=54	(≥5), 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=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; SGRQ, 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 = (4×0.5%+17×2.1%+12×2.3%+16×1.7%)/(4+17+12+16) = 1.9%; mean QLF change at Week 48 = (3×0.7%+15×1.9%+11×1.9%+20×5.5%)/(3+15+11+20) = 3.3%. For improvement of one parameter, mean QLF change at Week 24 = (11× -1.3%+4×0.5%+31×0.9%+12×2.3%)/(11+4+31+12) = 0.7%%; mean QLF change at Week 48 = (11×0.6%+3×0.7%+24×0.3%+11×1.9%)/(11+3+24+11) = 0.8%.

Note: The discordant changes when one 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 ±1%,

Supplemental table 3. Relationship of QLF as a percentage and a volume with MCID of SGRQ and ppFVC at Weeks 24 and 48

Week 24														
	SGRQ							ppFVC						
		Unadjusted analysis		Adjusted analysis, mean (95% CI)	Unadjusted analysis		Adjusted analysis, mean (95% CI)		Unadjusted analysis		Adjusted analysis, mean (95% CI)	Unadjusted analysis		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)	QLF change, mL mean (95% CI)	ES	QLF change, mL mean (95% CI)
Combined group														
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, 4.84)	101.90 (70.30, 133.49)	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 (−0.97, 0.97)	37.23 (13.38, 61.08)	0.33	0.00 (−23.85, 23.85)
Improved ^a	48	1.00 (−0.32, 2.32)	0.22	0.51 (−0.81, 1.83)	31.27 (−0.47, 63.01)	0.29	10.14 (−21.60, 41.88)	20	−1.00 (−3.01, 1.01)	−0.23	−1.99 (−4.00, 0.02)	−18.46 (−67.92, 30.99)	−0.17	−55.69 (−105.15, −6.24)
Study 049														
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)	129.62 (76.20, 183.05)	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)	37.70 (−0.08, 75.48)	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 (−148.12, 29.08)	−0.56	−97.22 (−185.82, 8.62)
Study 067														
Worsened ^a	19	2.89 (1.47, 4.32)	0.98	2.15 (0.73, 3.58)	82.71 (39.77, 125.65)	0.93	54.69 (11.75, 97.63)	27	2.96 (1.79, 4.14)	1.00	2.27 (1.10, 3.45)	79.30 (42.23, 116.38)	0.85	42.56 (5.49, 79.76)

Stable ^a	34	0.74 (−0.33, 1.80)	0.24	0 (−1.07, 1.06)	28.02 (−4.08, 60.12)	0.30	0 (−32.10, 32.10)	42	0.69 (−0.25, 1.63)	0.23	0.00 (−0.94, 0.94)	36.74 (7.01, 66.46)	0.39	0.00 (−29.73, 29.73)
Improved ^a	26	0.77 (−0.45, 1.99)	0.25	0.03 (−1.19, 1.25)	31.53 (−5.18, 68.24)	0.35	3.51 (−33.2, 40.22)	12	0.08 (−1.68, 1.84)	0.03	−0.61 (−2.37, 1.15)	8.91 (−46.70, 64.52)	0.10	−27.84 (−83.44, 27.78)
Week 48														
	SGRQ							FVC						
		Unadjusted analysis		Adjusted analysis, mean (95% CI)	Unadjusted analysis		Adjusted analysis, mean (95% CI)		Unadjusted analysis		Adjusted analysis, mean (95% CI)	Unadjusted analysis		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)	QLF change, mL mean (95% CI)	ES	QLF change, mL mean (95% CI)
Combined group														
Worsened ^a	42	5.52 (3.82, 7.23)	1.01	2.30 (0.60, 4.01)	157.32 (115.54, 199.10)	1.17	80.75 (38.97, 122.53)	53	5.75 (4.37, 7.14)	1.14	4.27 (2.89, 5.66)	155.99 (119.52, 192.45)	1.18	107.61 (71.14, 144.07)
Stable ^a	54	3.22 (1.72, 4.73)	0.58	0 (−1.50, 1.51)	76.57 (39.72, 113.42)	0.57	0 (−36.85, 36.85)	62	1.48 (0.20, 2.76)	0.29	0.00 (−1.28, 1.28)	48.38 (14.67, 82.09)	0.36	0.00 (−33.71, 33.71)
Improved ^a	41	0.39 (−1.34, 2.12)	0.07	−2.83 (−4.56, −1.10)	22.14 (−20.15, 64.42)	0.17	−54.53 (−96.72, −12.15)	20	−0.65 (−2.90, 1.60)	−0.14	−2.13 (−4.38, 0.12)	−16.46 (−75.81, 42.90)	− 0.13	−64.84 (−124.19, −5.48)
Study 049														
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)	33	6.70 (4.78, 8.62)	1.24	5.97 (4.05, 7.89)	181.80 (127.09, 236.51)	1.18	169.32 (114.61, 224.03)
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)	12.48 (−54.53, 79.48)	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)	11	−1.73 (−5.05, 1.60)	−0.35	−2.46 (−5.78, 0.87)	−50.42 (−145.18, 44.34)	− 0.36	−62.90 (−157.66, 31.86)
Study 067														

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)	20	4.20 (2.16, 6.24)	0.96	2.30 (0.26, 4.34)	113.39 (67.81, 158.97)	1.16	45.26 (−0.32, 90.84)
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)	68.13 (35.90, 100.36)	0.68	0.00 (−32.23, 32.23)
Improved ^a	24	1.08 (−0.68, 2.85)	0.26	−0.67 (−2.43, 1.10)	52.33 (14.67, 89.99)	0.59	6.68 (−30.98, 44.34)	9	0.67 (−2.38, 3.71)	0.17	−1.23 (−4.28, 1.81)	25.06 (−42.90, 93.01)	0.28	−43.07 (−111.03, 24.88)

Note: Negative sign denotes decline in ppFVC.

CI, confidence interval; ES, effect size; FVC, forced vital capacity; MCID, minimum clinically important difference; ppFVC, percent-predicted forced vital capacity; QLF, quantitative lung fibrosis; SGRQ, St. George’s Respiratory Questionnaire.

^aWorsened: SGRQ change ≥5 points or ppFVC change ≤ −3.4%; stable: SGRQ change between −5 and 5 points or ppFVC change between −3.4% and 3.4%; improved: SGRQ change ≤ −5 points or ppFVC change ≥3.4%.