643	Online Supplementary Material
644	for
645	Post hoc Analysis of Clinical Outcomes in Placebo- and Pirfenidone-treated
646	Patients with IPF Stratified by BMI and Weight Loss
647	Stéphane Jouneau, Bruno Crestani, Ronan Thibault, Mathieu Lederlin, Laurent Vernhet,
648	Ming Yang, Elizabeth Morgenthien, Klaus-Uwe Kirchgaessler, Vincent Cottin

Table E1. Demographic and baseline characteristics by baseline BMI category in patients

650 from the pirfenidone arms of ASCEND and CAPACITY

		Baseline BMI	
Demographic/characteristic*	<25 kg/m ²	25–<30 kg/m ²	≥30 kg/m²
	n = 73	n = 265	n = 285
Age at randomization, years	69.8 (7.5)	68.2 (7.1)	65.6 (7.7)
Male, <i>n</i> (%)	42 (57.5)	215 (81.1)	206 (72.3)
White <i>, n</i> (%)	58 (79.5)	226 (85.3)	259 (90.9)
Weight at baseline, kg			
Male	69.0 (8.0)	84.0 (9.0)	102.8 (14.5)
Female	58.6 (7.3)	70.3 (6.1)	85.7 (11.4)
BMI at baseline			
Male	23.4 (1.5)	27.7 (1.4)	33.6 (3.2)
Female	23.2 (1.5)	27.5 (1.6)	33.8 (3.3)
HRCT diagnosis group at baseline	e, n (%)		
Definite UIP	71 (97.3)	247 (93.6) ⁺	256 (89.8)
Probable/possible UIP	2 (2.7)	17 (6.4) ⁺	27 (9.5)

Uncertain with UIP	0 (0)	0 (0)	2 (0.7)
Time from IPF diagnosis to	1.7 (1.1)	1.5 (1.1)	1.4 (1.0)
randomization, years			
Percent predicted FVC	72.5 (15.9)	72.3 (13.8)	70.7 (11.8)
FEV ₁ /FVC ratio	0.9 (0.1)	0.8 (0.0)	0.8 (0.0)
Percent predicted DLco	44.6 (10.4)	44.8 (9.9)	46.5 (10.3)
Baseline 6MWD, m	410.5 (99.0) [‡]	424.2 (95.5) ⁺	383.0 (86.2) [§]
Baseline SGRQ score	30.9 (12.2) [∥]	35.9 (17.6)**	40.6 (17.4)**
Supplemental oxygen use at	11 (15.1)	50 (18.9)	94 (33.0)
baseline <i>, n</i> (%)			
Smoking status at screening, n (%)		
Current	0 (0.0)	3 (1.1)	5 (1.8)
History	38 (52.1)	173 (65.3)	195 (68.4)
Never	35 (47.9)	89 (33.6)	85 (29.8)
*Data are presented as mean (SI	D) unless specified c	otherwise. [†] <i>n</i> = 264. [‡]	n = 71. [§] n = 282.

||n| = 32. **n = 127. +*n = 170. 6MWD, 6-min walk distance; BMI, body mass index;

DLco, carbon monoxide diffusing capacity; FEV₁, forced expiratory volume in 1 second;

FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic

- 655 pulmonary fibrosis; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire;
- 656 UIP, usual interstitial pneumonia.

657 **Table E2.** Sensitivity analysis of clinical outcomes at 1 year stratified by annualized percent change in body weight, excluding 19 patients with no

- 658 post-baseline body-weight measurement after Day 90, in patients from the placebo arms of ASCEND and CAPACITY, and all patients from
- 659 INSPIRE and RIFF (Cohort A)

	Ar	inualized percent change in body we	ight
Outcome	No loss	>0<5% loss	≥5% loss
	n = 841	n = 599	n = 99
Annualized change from baseline i	n percent predicted FVC, %*		
Observed, n	838	589	99
Estimate (95% CI)	-4.2 (-4.6, -3.8)	-5.5 (-6.0, -5.0)	-9.5 (-10.7, -8.2)
Difference (95% CI) ⁺		-1.3 (-1.9, -0.6)	-5.2 (-6.6, -3.9)
Annualized change from baseline i	n percent predicted DLco, % ^{*,‡}		
Observed, n	699	489	67
Estimate (95% CI)	-4.1 (-4.6, -3.7)	-5.2 (-5.7, -4.6)	-6.9 (-8.5, -5.3)
Difference (95% CI) ⁺		-1.0 (-1.7, -0.3)	-2.8 (-4.4, -1.1)

Annualized change from baseline in 6MWD, m*

Observed, n	839	589	99		
Estimate (95% CI)	-25.7 (-31.0, -20.4)	-37.3 (-43.8, -30.8)	-81.1 (-98.7, -63.6)		
Difference (95% CI) ⁺		-11.6 (-20.0, -3.2)	-55.5 (-73.8, -37.1)		
Annualized change from baseline i	n SGRQ total score ^{*,‡}				
Observed, n	699	487	67		
Estimate (95% CI)	3.5 (2.8, 4.2)	5.0 (4.2, 5.9)	9.6 (7.2, 12.0)		
Difference (95% CI) ⁺		1.5 (0.4, 2.6)	6.1 (3.5, 8.6)		
Absolute decline in percent predic	ted FVC ≥10% or death up to 1 yea	r post-randomization, %§			
Observed, n	838	589	99		
Estimate (95% CI)	8.0 (3.1, 12.8)	12.3 (6.9, 17.8)	21.9 (12.6, 31.1)		
Difference (95% CI) ⁺		4.3 (0.4, 8.2)	13.9 (4.9, 22.8)		
Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, % [§]					
Observed, n	837	589	99		
Estimate (95% CI)	8.8 (4.0, 13.6)	16.0 (10.7, 21.4)	37.4 (27.0, 47.8)		

Difference (95% CI) ⁺		7.2 (3.5, 11.0)	28.5 (18.6, 38.5)
Any all-cause hospitalization up to	1 year post-randomization, %§		
Observed, n	839	589	99
Estimate (95% CI)	19.3 (14.1, 24.6)	24.5 (18.8, 30.3)	39.7 (29.5, 49.9)
Difference (95% CI) ⁺		5.2 (1.2, 9.2)	20.4 (10.5, 30.2)
All-cause mortality up to 1 year po	st-randomization, %§		
Observed, n	839	589	99
Estimate (95% CI)	7.6 (2.8, 12.4)	10.4 (4.7, 16.2)	12.0 (3.1, 20.9)
Difference (95% CI) ⁺		2.9 (-1.5, 7.2)	4.4 (-4.0, 12.8)
Any treatment-emergent SAEs up	to 1 year post-randomization, %§		
Observed, n	839	589	99
Estimate (95% CI)	22.1 (16.6, 27.6)	25.4 (19.5, 31.3)	51.0 (40.4, 61.7)
Difference (95% CI) ⁺		3.3 (-0.9, 7.6)	28.9 (18.7, 39.2)

660 *Estimates (95% CI) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF

diagnosis, baseline oxygen use, baseline smoking status, annualized percent change category, time, and annualized percent change

662 category*time as fixed-effect covariates, with random intercept and random slope for time for each patient. ⁺Estimated difference from first

- 663 category. [‡]Excludes ASCEND study. [§]Estimates (95% CI) based on logistic regression with study, age, sex, race, baseline HRCT status, years since
- 664 IPF diagnosis, baseline oxygen use, baseline smoking status, and annualized percent change in body-weight category as model factors.
- 665 6MWD, 6-min walk distance; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution
- 666 computed tomography; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire.

Table E3. Clinical outcomes at 1 year stratified by baseline BMI category in patients from the pirfenidone arms of ASCEND and CAPACITY

		Baseline BMI	
Outcome	<25 kg/m ²	25-<30 kg/m ²	≥30 kg/m²
	n = 73	n = 265	n = 285
Annualized change from baselin	e in percent predicted FVC, %*		
Observed, n	73	264	285
Estimate (95% CI)	-4.3 (-5.7, -2.9)	-4.4 (-5.1, -3.7)	-3.6 (-4.3, -3.0)
Difference (95% Cl) [†]		-0.1 (-1.7, 1.4)	0.7 (-0.8, 2.2)
Annualized change from baselin	e in percent predicted DLco, % ^{*,‡}		
Observed, n	33	134	177
Estimate (95% CI)	-4.8 (-6.7, -2.9)	-5.5 (-6.4, -4.6)	-5.0 (-5.84.3)
Difference (95% CI) ⁺		-0.7 (-2.8, 1.4)	-0.2 (-2.3, 1.8)

Annualized change from baseline in 6MWD, m*				
73	264	285		
-22.1 (-41.2, -3.0)	-26.5 (-36.2, -16.8)	-25.2 (-34.3, -16.2)		
	-4.4 (-25.8, 17.1)	-3.1 (-24.2, 18.0)		
e in SGRQ total score ^{*,‡}				
33	134	177		
-0.8 (-4.1, 2.4)	4.5 (2.8, 6.1)	2.8 (1.4, 4.1)		
	5.3 (1.7, 9.0)	3.6 (0.0, 7.1)		
Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, % ^{§,∥}				
73	264	285		
3.3 (0.7, 14.6)	5.4 (1.7, 16.3)	2.9 (0.8, 9.7)		
	2.1 (-9.8, 13.3)	-0.4 (-11.9, 6.8)		
	e in 6MWD, m* 73 -22.1 (-41.2, -3.0) e in SGRQ total score*,‡ 33 -0.8 (-4.1, 2.4) dicted FVC ≥10% or death up to 1 y 73 3.3 (0.7, 14.6)	e in 6MWD, m* 73 264 -22.1 (-41.2, -3.0) -26.5 (-36.2, -16.8) -4.4 (-25.8, 17.1) e in SGRQ total score*, [‡] 33 134 -0.8 (-4.1, 2.4) 4.5 (2.8, 6.1) 5.3 (1.7, 9.0) dicted FVC ≥10% or death up to 1 year post-randomization, % ^{§,} 73 264 3.3 (0.7, 14.6) 5.4 (1.7, 16.3) 2.1 (-9.8, 13.3)		

Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, % ^{§,∥}				
Observed, n	73	264	285	
Estimate (95% CI)	11.9 (4.8, 26.7)	13.3 (6.9, 24.1)	7.8 (3.8, 15.5)	
Difference (95% CI) [†]		1.3 (-14.8, 14.3)	-4.1 (-19.4, 6.4)	
Any all-cause hospitalization up	to 1 year post-randomization, %§			
Observed, n	73	264	285	
Estimate (95% CI)	12.4 (5.7, 24.8)	14.7 (8.4, 24.5)	16.1 (9.4, 26.0)	
Difference (95% CI) [†]		2.4 (-11.6, 14.2)	3.7 (-10.4, 15.7)	
All-cause mortality up to 1 year	post-randomization, % [§]			
Observed, n	73	264	285	
Estimate (95% CI)	1.9 (0.3, 11.8)	2.9 (0.7, 11.9)	1.3 (0.3, 6.3)	
Difference (95% CI) ⁺		1.1 (-9.1, 10.2)	-0.5 (-10.5, 4.7)	

Any treatment-emergent SAEs up to 1 year post-randomization, %§

Observed, n	73	264	285
Estimate (95% CI)	18.3 (9.5, 32.4)	18.0 (10.9, 28.3)	18.7 (11.5, 28.8)
Difference (95% CI) ⁺		-0.3 (-16.1, 13.2)	0.3 (-15.4, 13.8)

⁶⁶⁸ *Estimates (95% CI) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF

669 diagnosis, baseline oxygen use, baseline smoking status, baseline BMI category, time, and baseline BMI category*time as fixed-effect covariates,

670 with random intercept and random slope for time for each patient. [†]Estimated difference from first category. [‡]Excludes ASCEND study.

⁶⁷¹ [§]Estimates (95% CI) based on logistic regression with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use,

672 baseline smoking status, and baseline BMI category as model factors. Endpoint was derived from estimated annual change in percent predicted

673 FVC for each patient based on a simple random slopes and intercepts model. 6MWD, 6-min walk distance; BMI, body mass index; CI, confidence

- 674 interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic
- 675 pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire.

Table E4. Clinical outcomes at 1 year stratified by annualized percent change in body weight in patients from the pirfenidone arms of ASCEND

677 and CAPACITY

	Anr	nualized percent change in body we	ight
Outcome	No weight loss	>0-<5% loss	≥5% loss
	n = 374	<i>n</i> = 165	<i>n</i> = 84
Annualized change from baselin	e in percent predicted FVC, %*		
Observed, n	373	165	84
Estimate (95% CI)	-3.5 (-4.0, -2.9) [‡]	-4.1 (-5.0, -3.2)	-6.8 (-8.1, -5.5)
Difference (95% CI) ⁺		-0.6 (-1.7, 0.4)	-3.4 (-4.8, -1.9)
Annualized change from baselin	e in percent predicted DLco, % ^{*,‡}		
Observed, n	223	89	32
Estimate (95% CI)	-4.6 (-5.2, -3.9)	-5.6 (-6.7, -4.4)	-9.1 (-11.1, -7.1)
Difference (95% CI) ⁺		-1.0 (-2.4, 0.3)	-4.5 (-6.7, -2.4)

Annualized change from baseline in 6MWD, m*						
Observed, n	373	165	84			
Estimate (95% CI)	-18.0 (-25.8, -10.2)	-25.2 (-37.2, -13.2)	-67.5 (-86.1, -49.0)			
Difference (95% CI) ⁺		-7.2 (-21.5, 7.1)	-49.6 (-69.6, -29.5)			
Annualized change from baselin	e in SGRQ total score ^{*, ‡}					
Observed, n	223	89	32			
Estimate (95% CI)	2.4 (1.2, 3.7)	3.6 (1.6, 5.6)	6.6 (3.1, 10.1)			
Difference (95% Cl) ⁺		1.2 (-1.2, 3.5)	4.2 (0.5, 7.9)			
Absolute decline in percent prec	Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, % ^{§, ∥}					
Observed, n	373	165	84			
Estimate (95% CI)	2.4 (0.7, 7.9)	4.3 (1.2, 14.0)	14.6 (4.4, 39.0)			
Difference (95% Cl) ⁺		1.9 (-4.5, 11.8)	12.2 (0.6, 36.6)			

Relative decline in percent predicted FVC \geq 10% or death up to 1 year post-randomization, % ^{§,}						
Observed, n	373	165	84			
Estimate (95% CI)	5.9 (2.9, 12.0)	12.1 (5.8, 23.3)	34.8 (18.8, 55.2)			
Difference (95% CI) [†]		6.1 (-2.5, 17.7)	28.8 (11.8, 49.4)			
Any all-cause hospitalization up to 1 year post-randomization, %§						
Observed, n	373	165	84			
Estimate (95% CI)	11.3 (6.4, 19.0)	20.3 (11.7, 32.8)	26.2 (14.4, 42.8)			
Difference (95% CI) [†]		9.0 (-2.5, 22.5)	14.9 (0.9, 32.2)			
All-cause mortality up to 1 year post-randomization, %§						
Observed, n	373	165	84			
Estimate (95% CI)	1.4 (0.3, 6.1)	2.1 (0.4, 9.5)	6.0 (1.3, 24.2)			
Difference (95% CI) ⁺		0.7 (-4.3, 8.2)	4.6 (-2.1, 22.8)			

	Any treatment-emergent SAEs up to 1 year post-randomization, %§					
	Observed, n	373	165	84		
	Estimate (95% CI)	14.0 (8.4, 22.3)	22.5 (13.6, 34.9)	35.3 (21.5, 52.1)		
	Difference (95% CI) [†]		8.6 (-3.6, 22.1)	21.3 (5.2, 39.0)		
678	*Estimates (95% CIs) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF					
679	diagnosis, baseline oxygen use, baseline smoking status, annualized percent change in body-weight category, time, and annualized percent					
680	change in body-weight category*time as fixed-effect covariates, with random intercept and random slope for time for each patient. [†] Estimated					
681	difference from first category. [‡] Excludes ASCEND study. [§] Estimates (95% CIs) based on logistic regression with study, age, sex, race, baseline					
682	HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, and annualized percent change in body-weight category as					
683	model factors. ^{II} Endpoint was derived from estimated annual change in percent predicted FVC for each patient based on a simple random slopes					
684	and intercepts model. 6MWD, 6-min walk distance; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity;					
685	HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George's Respiratory					
686	Questionnaire.					

Figure E1. Sensitivity analysis of time to first all-cause hospitalization up to 1 year
post-randomization (with death as competing risk), stratified by annualized percent change
in body-weight categories, in patients from the placebo arms of ASCEND and CAPACITY, and
all patients from INSPIRE and RIFF (Cohort A).

