Supplementary Material

Figure S1. Annual rate of decline in forced vital capacity by baseline GAP stage (I, II, III)

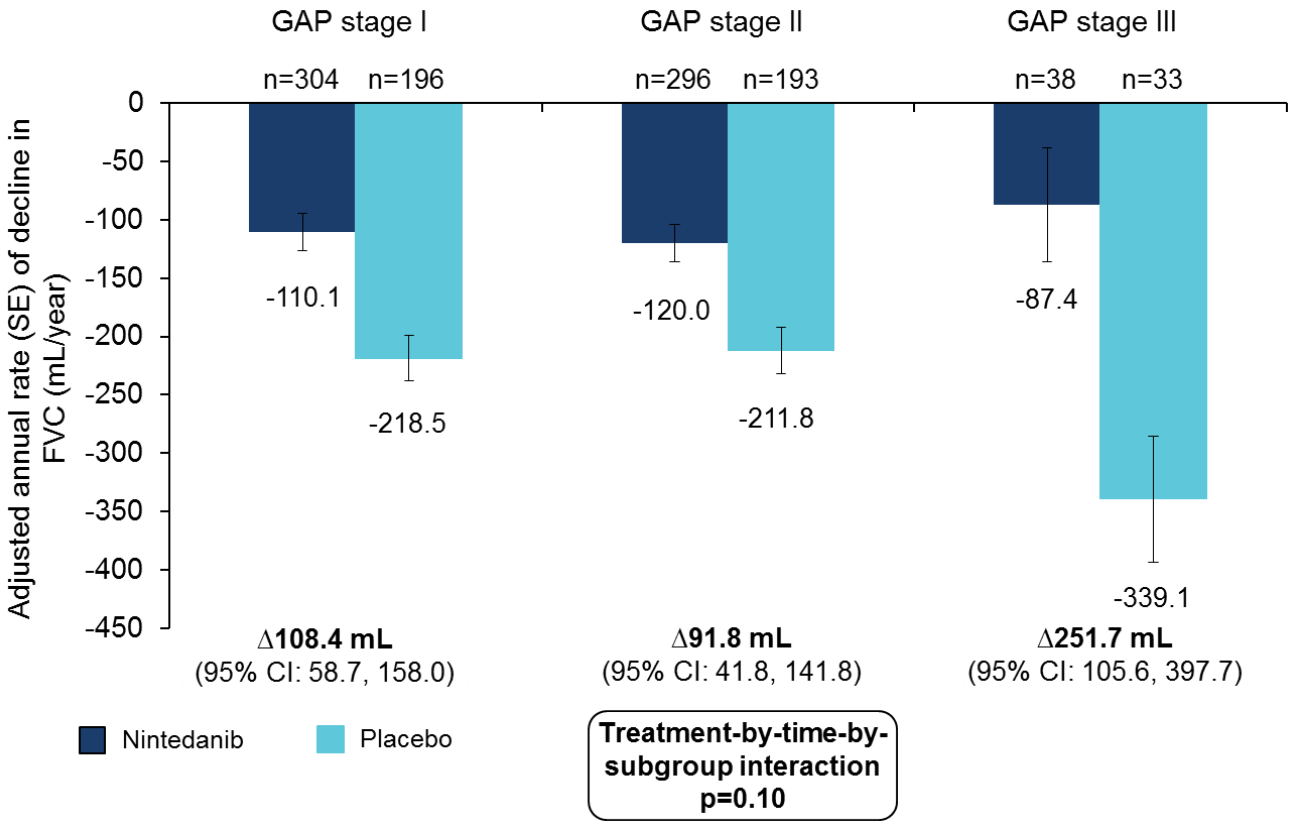

Figure S2. Change from baseline in SGRQ total score by subgroup at week 52 by baseline GAP stage (I, II, III)

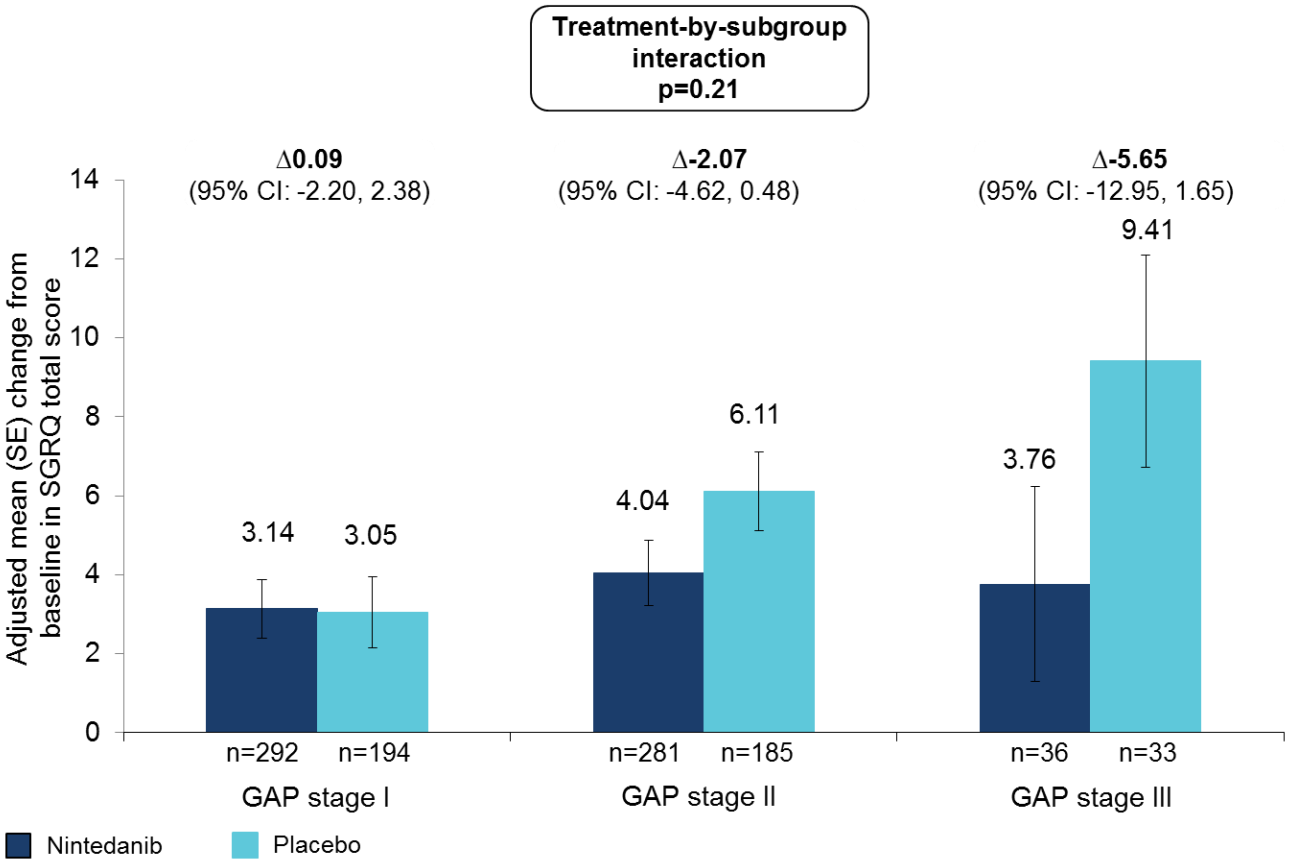

Table S1. GAP index and GAP stage at baseline

GAP index	Nintedanib	Placebo	Total	GAP stage	Total
8	0	0	0	**III**	71 (6.7)
7	0	0	0		
6	38 (6.0)	33 (7.8)	71 (6.7)		
5	108 (16.9)	76 (18.0)	184 (17.3)	**II**	489 (46.1)
4	188 (29.5)	117 (27.7)	305 (28.7)		
3	176 (27.6)	116 (27.4)	292 (27.5)	**I**	500 (47.1)
2	91 (14.3)	57 (13.5)	148 (13.9)		
1	30 (4.7)	21 (5.0)	51 (4.8)		
0	7 (1.1)	2 (0.5)	9 (0.8)		
Missing	0 (0.0)	1 (0.2)	1 (0.1)	**Missing**	1 (0.1)
Total	638 (100)	423 (100)	1061 (100)	**Total**	1061 (100)

Data shown are n (%).

Table S2. FVC % predicted and DLco % predicted by baseline GAP stage

GAP stage I	DLco % predicted					
	≥60 n (%)	≥50 n (%)	≥40 n (%)	≥30 n (%)	<30 n (%)	All n (%)
FVC % predicted						
≥100	52 (10.4)	82 (16.4)	107 (21.4)	112 (22.4)	1 (0.2)	113 (22.6)
≥90	80 (16.0)	129 (25.8)	175 (35.0)	186 (37.2)	3 (0.6)	189 (37.8)
≥80	123 (24.6)	211 (42.2)	289 (57.8)	317 (63.4)	3 (0.6)	320 (64.0)
≥70	138 (27.6)	252 (50.4)	354 (70.8)	399 (79.8)	4 (0.8)	403 (80.6)
≥60	151 (30.2)	281 (56.2)	407 (81.4)	467 (93.4)	5 (1.0)	472 (94.4)
≥50	156 (31.2)	290 (58.0)	426 (85.2)	494 (98.8)	6 (1.2)	500 (100.0)
<50	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All	156 (31.2)	290 (58.0)	426 (85.2)	494 (98.8)	6 (1.2)	500 (100.0)
GAP stage II/III						
FVC % predicted						
≥100	0 (0.0)	7 (1.3)	20 (3.6)	30 (5.4)	1 (0.2)	31 (5.5)
≥90	0 (0.0)	21 (3.8)	56 (10.0)	83 (14.8)	2 (0.4)	85 (15.2)
≥80	0 (0.0)	39 (7.0)	99 (17.7)	158 (28.2)	7 (1.3)	165 (29.5)
≥70	8 (1.4)	71 (12.7)	170 (30.4)	280 (50.0)	17 (3.0)	297 (53.0)
≥60	16 (2.9)	99 (17.7)	245 (43.8)	415 (74.1)	34 (6.1)	449 (80.2)
≥50	17 (3.0)	111 (19.8)	281 (50.2)	507 (90.5)	48 (8.6)	555 (99.1)
<50	0 (0.0)	1 (0.2)	2 (0.4)	5 (0.9)	0 (0.0)	5 (0.9)
All	17 (3.0)	112 (20.0)	283 (50.5)	512 (91.4)	48 (8.6)	560 (100.0)

Table S3. Proportions of patients with disease progression over 52 weeks and hazard ratio for time to first event by baseline GAP stage (I, II, III)

	GAP stage I		GAP stage II		GAP stage III	
	Nintedanib (n=304)	**Placebo (n=196)**	**Nintedanib (n=296)**	**Placebo (n=193)**	**Nintedanib (n=38)**	**Placebo (n=33)**
Absolute decline in FVC ≥10% predicted or death, n (%)	75 (24.7)	78 (39.8)	87 (29.4)	78 (40.4)	11 (28.9)	19 (57.6)
Hazard ratio (95% CI)	0.59 (0.43, 0.81)		0.65 (0.47, 0.88)		0.38 (0.17, 0.84)	
Treatment-by-subgroup interaction	p=0.44					
Criterion reached first, n (%)						
Absolute decline in FVC ≥10% predicted	69 (22.7)	75 (38.3)	71 (24.0)	64 (33.2)	8 (21.1)	14 (42.4)
Death	6 (2.0)	3 (1.5)	16 (5.4)	14 (7.3)	3 (7.9)	5 (15.2)
Absolute decline in FVC ≥5% predicted or death, n (%)	156 (51.3)	142 (72.4)	157 (53.0)	135 (69.9)	17 (44.7)	25 (75.8)
Hazard ratio (95% CI)	0.58 (0.46, 0.73)		0.65 (0.52, 0.83)		0.57 (0.30, 1.07)	
Treatment-by-subgroup interaction	p=0.49					
Criterion reached first, n (%)						
Absolute decline in FVC ≥5% predicted	154 (50.7)	141 (71.9)	148 (50.0)	127 (65.8)	15 (39.5)	23 (69.7)
Death	2 (0.7)	1 (0.5)	9 (3.0)	8 (4.1)	2 (5.3)	2 (6.1)

Table S4. Proportion of patients with an acute exacerbation and hazard ratio for time to first event by baseline GAP stage (I, II, III)

	GAP stage I		**GAP stage II**		**GAP stage III**	
	Nintedanib (n=304)	**Placebo (n=196)**	**Nintedanib (n=296)**	**Placebo (n=193)**	**Nintedanib (n=33)**	**Placebo (n=38)**
Patients with ≥1 acute exacerbation, n (%)	5 (1.6)	10 (5.1)	22 (7.4)	15 (7.8)	4 (10.5)	6 (18.2)
Hazard ratio (95% CI)	0.32 (0.11, 0.93)		0.95 (0.49, 1.83)		0.45 (0.12, 1.71)	
Treatment-by-subgroup interaction	p=0.25					

Table S5. Change from baseline in SGRQ domain score at week 52 by baseline GAP stage

	GAP stage I		GAP stage II/III	
	Nintedanib (n=304)	**Placebo (n=196)**	**Nintedanib (n=334)**	**Placebo (n=226)**
SGRQ symptoms, n	299	195	324	220
Change from baseline, adjusted mean (SE)	1.86 (1.11)	3.88 (1.37)	1.76 (1.06)	3.34 (1.29)
Nintedanib versus placebo difference, adjusted mean (95% CI)	-2.01 (-5.46, 1.44)		-1.58 (-4.85, 1.69)	
Treatment-by-subgroup interaction	p=0.90			
SGRQ activity, n	295	195	322	218
Change from baseline, adjusted mean (SE)	3.81 (0.90)	4.45 (1.10)	4.71 (0.86)	8.35 (1.05)
Nintedanib versus placebo difference, adjusted mean (95% CI)	-0.63 (-3.42, 2.15)		-3.64 (-6.32, -0.97)	
Treatment-by-subgroup interaction	p=0.09			
SGRQ impact, n	293	196	318	220
Change from baseline, adjusted mean (SE)	3.18 (0.85)	2.90 (1.04)	4.52 (0.92)	6.74 (1.11)
Nintedanib versus placebo difference, adjusted mean (95% CI)	0.28 (-2.35, 2.91)		-2.22 (-5.05, 0.61)	
Treatment-by-subgroup interaction	p=0.12			

Table S6. Serious and fatal adverse events by baseline GAP stage

	GAP stage I		GAP stage II/III	
	Nintedanib (n=304)	**Placebo (n=196)**	**Nintedanib (n=334)**	**Placebo (n=226)**
Serious adverse event(s)*	60 (19.7)	45 (23.0)	134 (40.1)	81 (35.8)
Most frequent serious adverse event(s)†				
Progression of IPF‡	11 (3.6)	10 (5.1)	31 (9.3)	29 (12.8)
Pneumonia	8 (2.6)	2 (1.0)	15 (4.5)	14 (6.2)
Pulmonary hypertension	3 (1.0)	1 (0.5)	8 (2.4)	8 (3.5)
Bronchitis	1 (0.3)	0 (0.0)	7 (2.1)	2 (0.9)
Respiratory failure	1 (0.3)	3 (1.5)	1 (0.3)	5 (2.2)
Fatal adverse event(s)	8 (2.6)	6 (3.1)	29 (8.7)	25 (11.1)
Most frequent fatal adverse event(s)§				
Pneumonia	0 (0.0)	0 (0.0)	5 (1.5)	2 (0.9)
Progression of IPF‡	4 (1.3)	3 (1.5)	14 (4.2)	13 (5.8)

*An event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason. †Adverse events reported in >2% of patients in any of the subgroups shown. ‡Corresponds to MedDRA term 'IPF', which included disease worsening and acute exacerbations of IPF. MedDRA, Medical Dictionary for Regulatory Activities. §Fatal adverse events reported in >1% of patients in any of the subgroups shown.