Supplementary material

Supplementary Table 1. Comparison of anti-topoisomerase I antibody (ATA) status based on historical (local laboratory) information (or on central laboratory data if historical information was not available) and central laboratory data in the SENSCIS trial.

	ATA-positive based on historical information or on central laboratory data if historical information was not available		**ATA-negative based on historical information** or on central laboratory data if historical information was not available	
	Nintedanib (n=173)	**Placebo (n=177)**	**Nintedanib (n=115)**	**Placebo (n=111)**
ATA-positive based on central laboratory data, no. (%)	125 (72.3)	130 (73.5)	0	0
ATA-negative based on central laboratory data, no. (%)	0	2 (1.1)	86 (74.8)	89 (80.2)

Missing central laboratory data, no. (%)	48 (27.7)	45 (25.4)	29 (25.2)	22 (19.8)

Supplementary Table 2. Baseline characteristics of subgroups by ATA status at baseline in the SENSCIS trial.

	ATA-positive		ATA-negative	
	Nintedanib (n=173)	**Placebo (n=177)**	**Nintedanib (n=115)**	**Placebo (n=111)**
Female, no. (%)	137 (79.2)	137 (77.4)	84 (73.0)	75 (67.6)
Age, mean ± SD years	53.2 ± 12.0	52.3 ± 12.3	56.7 ± 11.2	55.0 ± 13.0
Body mass index, mean ± SD kg/m^2	25.8 ± 5.0	26.1 ± 5.2	26.2 ± 4.6	25.2 ± 5.0
Race, no. (%)*				
White	118 (68.2)	110 (62.1)	83 (72.2)	76 (68.5)
Asian	38 (22.0)	52 (29.4)	24 (20.9)	29 (26.1)
Black/African-American	13 (7.5)	11 (6.2)	7 (6.1)	5 (4.5)

American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander	2 (1.2)	2 (1.1)	1 (0.9)	1 (0.9)
Time since onset of first non-Raynaud symptom, median years	3.5	3.6	3.4	3.3
Diffuse cutaneous SSc, no. (%)	106 (61.3)	102 (57.6)	47 (40.9)	44 (39.6)
mRSS†, mean ± SD	12.5 ± 9.4	11.6 ± 8.9	9.5 ± 8.6	9.9 ± 8.5
SGRQ total score‡, mean ± SD	41.8 ± 20.5	39.0 ± 21.5	39.2 ± 19.6	40.0 ± 20.1
Taking mycophenolate (mofetil or sodium), no. (%)	84 (48.6)	88 (49.7)	55 (47.8)	52 (46.8)
Extent of fibrotic ILD on HRCT§, mean ± SD %	37.1 ± 22.1	36.0 ± 21.3	36.3 ± 21.3	33.9 ± 19.8
FVC, mean ± SD mL	2428 ± 792	2489 ± 756	2505 ± 644	2624 ± 900
FVC, mean ± SD % predicted	70.7 ± 16.5	72.0 ± 15.3	74.9 ± 16.9	73.8 ± 18.5

DLco, mean ± SD % predicted[¶]	52.7 ± 15.6	53.1 ± 14.9	53.0 ± 14.3	53.4 ± 15.4

*Data from patients who selected one race. Four patients ticked more than one box. [†]2 patients had a missing value. [‡]11 patients had a missing value. [§]Assessed in the whole lung to nearest 5% by central review. Pure (non-fibrotic) ground glass opacity was not included. [¶]Corrected for hemoglobin; 7 patients had a missing value. ATA = anti-topoisomerase I antibody; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; mRSS = modified Rodnan skin score; SSc = systemic sclerosis; SGRQ = St. George's Respiratory Questionnaire.

Supplementary Table 3. Baseline characteristics of subgroups by mRSS <18 and ≥18 at baseline in the SENSCIS trial.

	mRSS <18		mRSS ≥18	
	Nintedanib (n=219)	**Placebo (n=226)**	**Nintedanib (n=69)**	**Placebo (n=60)**
Female, no. (%)	169 (77.2)	161 (71.2)	52 (75.4)	49 (81.7)
Age, mean ± SD years	55.3 ± 11.5	54.6 ± 12.0	52.2 ± 12.3	48.6 ± 13.7
Body mass index, mean ± SD kg/m^2	26.3 ± 4.7	26.1 ± 5.1	24.9 ± 5.0	24.4 ± 4.6
Race, no. (%)*				
White	151 (68.9)	144 (63.7)	50 (72.5)	40 (66.7)
Asian	49 (22.4)	68 (30.1)	13 (18.8)	13 (21.7)
Black/African-American	14 (6.4)	11 (4.9)	6 (8.7)	5 (8.3)

American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander	3 (1.4)	1 (0.4)	0 (0.0)	2 (3.3)
Time since onset of first non-Raynaud symptom, median, years	3.3	3.2	3.8	4.4
Diffuse cutaneous SSc, no. (%)	84 (38.4)	84 (37.2)	69 (100)	60 (100)
ATA-positive[†], no. (%)	122 (55.7)	139 (61.5)	51 (73.9)	36 (60.0)
mRSS, mean ± SD	7.2 ± 5.2	7.3 ± 4.8	24.5 ± 6.2	24.7 ± 6.6
SGRQ total score[‡], mean ± SD	39.6 ± 19.4	37.8 ± 20.3	44.4 ± 22.2	45.7 ± 21.7
Taking mycophenolate (mofetil or sodium), no. (%)	96 (43.8)	107 (47.3)	43 (62.3)	32 (53.3)
Extent of fibrotic ILD on HRCT[§], mean ± SD %	36.9 ± 21.7	33.4 ± 19.9	36.4 ± 22.1	41.3 ± 22.5
FVC, mean ± SD mL	2491 ± 746	2569 ± 802	2354 ± 697	2419 ± 865

FVC, mean ± SD % predicted	73.9 ± 17.2	73.4 ± 16.6	67.4 ± 14.3	69.3 ± 16.1
DLco, mean ± SD % predicted¶	53.3 ± 14.6	53.7 ± 15.2	51.5 ± 16.6	51.6 ± 14.7

Baseline mRSS data were not available for two patients in the placebo group. *Data from patients who selected one race. Four patients ticked more than one box. †As reported on the SSc-related medical history page of the case report form. ‡11 patients had a missing value. §Assessed in the whole lung to nearest 5% by central review. Pure (non-fibrotic) ground glass opacity was not included. ¶Corrected for hemoglobin; 7 patients had a missing value. ATA = anti-topoisomerase I antibody; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; mRSS = modified Rodnan skin score; SSc = systemic sclerosis; SGRQ = St. George's Respiratory Questionnaire.

Supplementary Table 4. Baseline characteristics in patients classified by investigators as having limited cutaneous SSc and diffuse cutaneous SSc in the SENSCIS trial.

	Limited cutaneous SSc		Diffuse cutaneous SSc	
	Nintedanib (n=135)	**Placebo (n=142)**	**Nintedanib (n=153)**	**Placebo (n=146)**
Female, no. (%)	102 (75.6)	102 (71.8)	119 (77.8)	110 (75.3)
Age, mean ± SD years	56.6 ± 11.5	55.8 ± 11.9	52.9 ± 11.8	51.0 ± 12.8
Body mass index, mean ± SD kg/m^2	26.8 ± 4.9	25.7 ± 4.9	25.2 ± 4.6	25.9 ± 5.4
Race, no. (%)*				
White	90 (66.7)	92 (64.8)	111 (72.5)	94 (64.4)
Asian	34 (25.2)	44 (31.0)	28 (18.3)	37 (25.3)
Black/African-American	7 (5.2)	5 (3.5)	13 (8.5)	11 (7.5)

American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander	2 (1.5)	0 (0.0)	1 (0.7)	3 (2.1)
Time since onset of first non-Raynaud symptom, median, years	3.1	2.6	3.7	4.3
ATA-positive[†], no. (%)	67 (49.6)	75 (52.8)	106 (69.3)	102 (69.9)
mRSS[‡], mean ± SD	4.9 ± 4.2	5.4 ± 4.1	17.0 ± 8.7	16.3 ± 8.9
SGRQ total score[§], mean ± SD	38.0 ± 19.6	36.8 ± 20.0	43.2 ± 20.5	41.9 ± 21.6
Taking mycophenolate (mofetil or sodium), no. (%)	60 (44.4)	66 (46.5)	79 (51.6)	74 (50.7)
Extent of fibrotic ILD on HRCT[¶], mean ± SD %	38.6 ± 22.4	33.0 ± 19.8	35.3 ± 21.2	37.4 ± 21.5
FVC, mean ± SD mL	2512 ± 697	2570 ± 807	2411 ± 768	2512 ± 825
FVC, mean ± SD % predicted	75.0 ± 17.1	74.5 ± 16.5	70.0 ± 16.2	70.9 ± 16.5

DLco, mean ± SD % predicted[#]	52.5 ± 13.4	52.7 ± 14.7	53.1 ± 16.5	53.8 ± 15.4

*Data from patients who selected one race. Four patients ticked more than one box. [†]As reported on the SSc-related medical history page of the case report form. [‡]2 patients had a missing value. [§]11 patients had a missing value. [¶]Assessed in the whole lung to nearest 5% by central review. Pure (non-fibrotic) ground glass opacity was not included. [#]Corrected for hemoglobin; 7 patients had a missing value. ATA = anti-topoisomerase I antibody; FVC = forced vital capacity; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; mRSS = modified Rodnan skin score; SSc = systemic sclerosis; SGRQ = St. George's Respiratory Questionnaire.

Supplementary Table 5. Rate of decline in FVC and change from baseline in mRSS at week 52 in subgroups by mRSS (≤10, >10 to <22 and ≥22) at baseline in the SENSCIS trial.

	mRSS ≤10		mRSS >10 to <22		mRSS ≥22	
	Nintedanib (n=155)	**Placebo (n=160)**	**Nintedanib (n=92)**	**Placebo (n=91)**	**Nintedanib (n=41)**	**Placebo (n=35)**
Annual rate of decline in FVC (mL/year)*						
Rate of decline in FVC (mL/year) over 52 weeks, adjusted rate (SE)	-49.2 (18.6)	-86.8 (18.1)	-80.7 (24.7)	-82.0 (24.4)	3.9 (38.1)	-143.9 (38.4)
Adjusted difference vs placebo (95% CI)	37.6 (-13.6, 88.7)		1.3 (-67.0, 69.5)		147.8 (41.6, 254.0)	
P value for treatment-by-time-by-subgroup interaction	0.07					

Change from baseline in mRSS at week 52						
Change in mRSS at week 52, adjusted mean (SE)	-2.4 (0.5)	-1.9 (0.5)	-1.8 (0.5)	-2.2 (0.5)	-2.1 (1.2)	-1.5 (1.2)
Adjusted difference vs placebo (95% CI)	-0.4 (-1.4, 0.6)		0.3 (-1.0, 1.6)		-0.5 (-2.6, 1.5)	
P value for treatment-by-visit-by-subgroup interaction			0.63			

Baseline mRSS data were not available for two patients in the placebo group and these patients were excluded from all analyses shown. *Post-baseline FVC data were not available for one patient with mRSS >10 to <22 in the nintedanib group and this patient was excluded from the analysis. FVC = forced vital capacity; mRSS = modified Rodnan skin score.

Supplementary Table 6. Spearman correlation coefficients between FVC at baseline and change in mRSS at week 52, mRSS at baseline and change in FVC at week 52, and changes from baseline in mRSS and FVC at week 52 in the SENSCIS trial.

	FVC (mL) at baseline and change in mRSS at week 52		mRSS at baseline and change in FVC (mL) at week 52		Changes from baseline in mRSS and FVC (mL) at week 52	
	N	Spearman correlation coefficient (95% CI)	N	Spearman correlation coefficient (95% CI)	N	Spearman correlation coefficient (95% CI)
Nintedanib	247	0.11 (-0.01, 0.23)	241	-0.08 (-0.20, 0.05)	238	-0.07 (-0.19, 0.06)
Placebo	254	0.12 (-0.00, 0.24)	257	-0.15 (-0.27, -0.03)	252	0.03 (-0.09, 0.15)

FVC = forced vital capacity; mRSS = modified Rodnan skin score.

Supplementary Table 7. Rate of decline in FVC; proportions of patients with worsening of FVC and stable or improved FVC; and change from baseline in mRSS at week 52 in patients classified by investigators as having limited or diffuse cutaneous SSc in the SENSCIS trial.

	Limited cutaneous SSc		Diffuse cutaneous SSc	
	Nintedanib (n=135)	**Placebo (n=142)**	**Nintedanib (n=153)**	**Placebo (n=146)**
Annual rate of decline in FVC (mL/year)*				
Rate of decline in FVC (mL/year) over 52 weeks, adjusted rate (SE)	-49.1 (19.8)	-74.5 (19.2)	-55.4 (19.3)	-112.0 (19.1)
Adjusted difference vs placebo (95% CI)	25.3 (-28.9, 79.6)		56.6 (3.2, 110.0)	
P value for treatment-by-time-by-subgroup interaction	0.42			
Proportions of patients who met proposed thresholds for worsening of FVC and stable or improved FVC† at week 52*				

Decrease in FVC ≥3.3% predicted, no. (%)	40 (29.9)	55 (38.7)	59 (38.6)	71 (48.6)
Odds ratio vs placebo (95% CI)	0.68 (0.41, 1.11)		0.66 (0.42, 1.05)	
P value for treatment-by-subgroup interaction	0.96			
Increase in FVC or decrease in FVC <3.3% predicted, no. (%)	94 (70.1)	87 (61.3)	94 (61.4)	75 (51.4)
Odds ratio vs placebo (95% CI)	1.48 (0.90, 2.44)		1.51 (0.95, 2.39)	
P value for treatment-by-subgroup interaction	0.96			
Change from baseline in mRSS at week 52[§]				
Change in mRSS at week 52, adjusted mean (SE)	-2.7 (0.4)	-2.5 (0.4)	-1.6 (0.4)	-1.5 (0.4)
Adjusted difference vs placebo (95% CI)	-0.3 (-1.3, 0.8)		-0.2 (-1.2, 0.8)	
P value for treatment-by-visit-by-subgroup interaction	0.94			

*Post-baseline FVC data were not available for one patient with limited cutaneous SSc in the nintedanib group; this patient was excluded from the analysis. †Proposed thresholds for minimal clinically important differences for worsened FVC and stable or improved FVC based on estimates derived from Scleroderma Lung Studies I and II anchored to the health transition question from

the Medical Outcomes Short Form-36 (1). §Baseline mRSS data were not available for two patients with diffuse cutaneous SSc in the placebo group; these patients were excluded from the analysis. FVC = forced vital capacity; mRSS = modified Rodnan skin score; SSc = systemic sclerosis.

References

1. Kafaja S, Clements PJ, Wilhalme H, Tseng CH, Furst DE, Kim GH, et al. Reliability and minimal clinically important differences of forced vital capacity: results from the Scleroderma Lung Studies (SLS-I and SLS-II). Am J Respir Crit Care Med 2018;197:644–52.