Kuwana Masataka (Orcid ID: 0000-0001-8352-6136)
Denton Christopher P (Orcid ID: 0000-0003-3975-8938)
Distler Jörg H.W. (Orcid ID: 0000-0001-7408-9333)
Khanna Dinesh (Orcid ID: 0000-0003-1412-4453)
Mayes Maureen D. (Orcid ID: 0000-0001-5070-2535)
Volkmann Elizabeth R. (Orcid ID: 0000-0003-3750-6569)
Distler Oliver (Orcid ID: 0000-0002-2413-1959)

Short title: Subgroups by autoantibody status and skin score in the SENSCIS trial

Title: Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: subgroup analyses by autoantibody status and skin score

Prof Masataka Kuwana MD,[1] Prof Yannick Allanore PhD,[2] Prof Christopher P Denton PhD,[3] Prof Jörg HW Distler MD,[4] Prof Virginia Steen MD,[5] Prof Dinesh Khanna MD,[6] Prof Marco Matucci-Cerinic MD, PhD,[7] Prof Maureen D Mayes MD,[8] Elizabeth R Volkmann MD,[9] Corinna Miede MSc,[10] Martina Gahlemann MD,[11] Manuel Quaresma Lic,[12] Margarida Alves MD,[12] Prof Oliver Distler MD[13]

[1]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [2]Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France; [3]University College London Division of Medicine, Centre for Rheumatology and Connective Tissue Diseases, London, UK; [4]University of Erlangen-Nuremberg, Erlangen, Germany; [5]Division of Rheumatology, Georgetown University, Washington, D.C., USA; [6]Department of Medicine, University of Michigan, Ann Arbor, MI, USA; [7]University of Florence, Department of Medicine, Florence, Italy; [8]Division of Rheumatology and Clinical Immunogenetics, University of Texas McGovern Medical School, Houston, TX, USA; [9]Department of Medicine, Division of Rheumatology, University of California, David Geffen School of Medicine, Los Angeles, CA, USA; [10]mainanalytics GmbH, Sulzbach (Taunus), Germany [11]Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; [12]Boehringer

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Ingelheim International GmbH, Ingelheim, Germany; [13]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland.

Corresponding author:

Masataka Kuwana, MD, Department of Allergy and Rheumatology, Nippon Medical School, Sendagi 1-1-5, Bunkyo-ku, Tokyo. Tel: +81-3-3822-2131. Email: kuwanam@nms.ac.jp

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Abstract

Objective: We used data from the SENSCIS trial to assess the effects of nintedanib versus placebo in subgroups of patients with SSc-ILD based on characteristics associated with progression of SSc-ILD in previous studies.

Methods: Patients with SSc-ILD were randomized to receive nintedanib or placebo, stratified by anti-topoisomerase I antibody (ATA) status. We assessed the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks in subgroups by baseline ATA status, modified Rodnan skin score (mRSS) (<18 versus ≥18), and SSc subtype (limited cutaneous SSc [lcSSc] versus diffuse cutaneous SSc [dcSSc]).

Results: At baseline, of 576 patients treated, 60.8% were ATA-positive, 51.9% had dcSSc, and 77.5% of 574 patients with mRSS data available had mRSS <18. The effect of nintedanib versus placebo on reducing the rate of decline in FVC (mL/year) was numerically more pronounced in patients who were ATA-negative (difference: 57.2 [95% CI -3.5, 118.0]) than ATA-positive (difference: 29.9 [-19.1, 78.8]), in patients who had mRSS ≥18 (difference: 88.7 [7.7, 169.8]) than mRSS <18 at baseline (difference: 26.4 [-16.8, 69.6]), and in patients with dcSSc (difference: 56.6 [3.2, 110.0]) than lcSSc (difference: 25.3 [-28.9, 79.6]), but exploratory interaction *P* values did not indicate heterogeneity in the effect of nintedanib versus placebo between these subgroups (*P* > 0.05 for all).

Conclusion: In patients with SSc-ILD, no heterogeneity was detected in the treatment effect of nintedanib in reducing the annual rate of decline in FVC across subgroups based on ATA status, mRSS, and SSc subtype.

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by progressive fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common manifestation of SSc and the leading cause of death in patients with SSc (2). Patients with progressive SSc-ILD have a poor outcome and need to be identified in clinical practice so that they can be managed appropriately (3-5).

In clinical practice, patients with SSc are classified into two subtypes based on the extent of skin involvement: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (6). The dcSSc subtype is associated with earlier onset of non-Raynaud symptoms (7), higher mortality (8) and a greater risk of developing ILD (7), but ILD is also a common cause of death in patients with lcSSc (9). The course of skin fibrosis in patients with dcSSc typically involves worsening early in the course of the disease followed by gradual improvement (10). Among patients with dcSSc in the European Scleroderma Trials and Research (EUSTAR) database, a high modified Rodnan skin score (mRSS) at baseline was a predictor of improvement in the mRSS over the next 12 months, independent of disease duration, and an upper mRSS threshold of 18–25 was proposed to enrich a cohort for patients with a progressive skin phenotype (11).

Specific autoantibody profiles have been associated with organ involvement and mortality in patients with SSc (8,12-15). Patients who are positive for anti-topoisomerase I antibody (ATA) have been reported to have a greater risk of developing clinically significant ILD (8,15). In the GENISOS cohort of 266 patients with early SSc, ATA positivity was associated with a greater rate of decline in forced vital capacity (FVC) over 3 years (16). In a single-centre analysis, among 505

patients who developed SSc-ILD, ATA positivity was predictive of developing FVC <70% predicted within 5 years of onset of SSc (17).

Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes involved in the progression of pulmonary fibrosis (18). In the SENSCIS trial in patients with SSc-ILD, nintedanib was associated with a significant reduction versus placebo in the rate of decline in FVC (mL/year) over 52 weeks, with no difference in the change from baseline in the mRSS (19). In addition, numerically lower proportions of patients treated with nintedanib versus placebo had declines in FVC >5% to ≤10% predicted and >10% predicted over 52 weeks (20). We used data from the SENSCIS trial to assess the progression of ILD, the progression of skin fibrosis, and the effects of nintedanib in subgroups by baseline ATA status, mRSS, and SSc subtype.

PATIENTS AND METHODS

Trial design and patients

The SENSCIS trial (NCT02597933) was a randomized, placebo-controlled trial conducted in 32 countries (19). The trial was conducted in accordance with the trial protocol, the principles of the Declaration of Helsinki, and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and was approved by local authorities. Written informed consent was obtained from all patients before study entry.

The design of the SENSCIS trial has been published, together with the trial protocol and statistical analysis plan (19). In brief, patients with SSc with onset of first non-Raynaud symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on a high-

resolution computed tomography (HRCT) scan (based on assessment of the whole lung), FVC ≥40% predicted and diffusing capacity of the lung for carbon monoxide (DLco) 30–89% predicted were enrolled. Patients on prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate. At screening, patients were classified as having lcSSc or dcSSc by the investigators. Patients were randomized 1:1 to receive nintedanib 150 mg bid or placebo, stratified by the presence of ATA (based on historical [local laboratory] information or on central laboratory data if historical information was not available). ATA was also detected at a central laboratory (using the BioPlex 2200 System bead assay).

Patients received blinded treatment until the last patient had reached week 52 but for ≤100 weeks. Patients who discontinued trial medication were asked to attend all scheduled visits and undergo examinations as originally planned. Spirometry was performed at baseline and at weeks 2, 4, 6, 12, 24, 36, and 52 in accordance with international guidelines (21). The mRSS was measured at baseline and at weeks 12, 24, 36, and 52. The mRSS evaluates a patient's skin thickness through palpation of 17 areas using a scale of 0 to 3 to give a maximum score of 51 (22,23).

Endpoints

Analyses conducted in the overall population of the SENSCIS trial have been described (19). Here we report the results of analyses in subgroups by baseline ATA status (based on historical [local laboratory] information, as reported in the case report form, or on central laboratory data if historical information was not available), mRSS (<18 vs ≥18, and ≤10 vs >10 to <22 vs ≥22), and SSc subtype (lcSSc vs

dcSSc). In these subgroups, we assessed the annual rate of decline in FVC (mL/year) over 52 weeks. In subgroups by baseline ATA status, mRSS <18 vs ≥18, and SSc subtype (lcSSc vs dcSSc), we also assessed the proportions of patients who met proposed thresholds for minimal clinically important differences (MCID) for stable or improved FVC (increase in FVC or absolute decrease <3.3% predicted) and worsened FVC (absolute decrease ≥3.3% predicted) at week 52, based on estimates derived from Scleroderma Lung Studies I and II anchored to the health transition question from the Medical Outcomes Short Form-36 (24). We also assessed the change from baseline in the mRSS at week 52 in the same subgroups. In the overall population, we assessed the correlations between FVC (mL) at baseline and change from baseline in mRSS at week 52, mRSS at baseline and change from baseline in FVC (mL) at week 52, and changes from baseline in mRSS and FVC (mL) at week 52. Finally, we assessed the rate of decline in FVC (mL/year) considering mRSS at baseline as a continuous variable.

Statistical analysis

All analyses were conducted in patients who received ≥1 dose of trial medication. The annual rate of decline in FVC (mL/year) was analyzed in the subgroups using a random coefficient regression model (with random slopes and intercepts) with fixed categorical effects of ATA status (ATA positive, ATA negative) and sex, fixed continuous effects of baseline FVC (mL), age, and height and including baseline−by−time, treatment−by−subgroup and treatment−by−subgroup−by−time interaction terms. The analysis was based on all measurements taken within the first 52 weeks, including those from patients who discontinued trial medication. The proportions of patients who met proposed thresholds for stable or improved FVC and

worsened FVC at week 52 were compared between treatment groups using a logistic regression model including treatment, ATA status, subgroup and treatment−by−subgroup interaction as terms in the model. Odds ratios were estimated for the independent effect of treatment within each subgroup. Missing values were imputed using a worst value carried forward approach. Subgroup analyses of change from baseline in the mRSS at week 52 were based on a mixed model for repeated measures (MMRM), with fixed categorical effects of ATA status, treatment−by−subgroup−by−visit interaction and a fixed continuous covariate of baseline mRSS−by−visit interaction. For every subgroup analysis, an exploratory interaction *P* value of an F-test (in random coefficient regression or MMRM analyses) or Wald test (in logistic regression analyses) of heterogeneity was calculated to evaluate potential heterogeneity in the treatment effect of nintedanib versus placebo between the subgroups, with no adjustment for multiple testing. Spearman correlation coefficients were calculated to analyze the correlations between FVC and mRSS described above. The rate of decline in FVC (mL/year) considering mRSS at baseline as a continuous variable was analyzed using a random coefficient regression model with fixed categorical effects of treatment, ATA status and sex, fixed continuous effects of baseline FVC (mL), age and height and including baseline FVC-by-time, treatment-by-time, treatment-by-baseline mRSS and treatment-by-baseline-mRSS-by-time interaction terms.

RESULTS

Patients

The baseline characteristics of the patients in the SENSCIS trial have been described (19). In the nintedanib and placebo groups, respectively, 173 (60.1%) and 177 (61.5%) patients were ATA-positive at baseline. ATA status based on historical information was generally consistent with that based on central laboratory data (Supplementary Table 1). Compared with ATA-negative patients, the subgroup of ATA-positive patients had a lower proportion of male patients, a greater proportion of patients with dcSSc, and a higher mean mRSS at baseline (Supplementary Table 2). Similar proportions of ATA-positive and ATA-negative patients were taking mycophenolate at baseline (49.1% and 47.3%, respectively).

Two patients in the placebo group did not have information on mRSS at baseline. Of 288 and 286 patients in the nintedanib and placebo groups, respectively, who had information on mRSS at baseline, 219 (76.0%) and 226 (79.0%) had an mRSS <18. All patients with an mRSS ≥18, and 37.8% of patients with an mRSS <18, were classified as having dcSSc. Compared to patients with an mRSS ≥18, patients with an mRSS <18 had a greater mean baseline FVC % predicted, and higher proportions were ATA-negative and male (Supplementary Table 3). A smaller proportion of patients with an mRSS <18 than ≥18 were taking mycophenolate at baseline (45.6% vs 58.1%). In the nintedanib and placebo groups, respectively, 153 (53.1%) and 146 (50.7%) of patients were classified as having dcSSc; their baseline characteristics are shown in Supplementary Table 4.

Outcomes in subgroups by ATA status

The adjusted annual rate (SE) of decline in FVC in the placebo group was consistent between patients who were ATA-positive and ATA-negative at baseline (-93.5 [17.3] mL/year and -93.1 [21.9] mL/year, respectively) (Figure 1A, Table 1). Analyses of the adjusted annual rates (SE) of decline in FVC in the placebo group that also adjusted

for use of mycophenolate at baseline were very similar (-93.4 [17.3] mL/year and -93.2 [21.9] mL/year in patients who were ATA-positive and ATA-negative at baseline, respectively). The effect of nintedanib vs placebo on reducing the annual rate of decline in FVC was numerically more pronounced in patients who were ATA-negative (difference: 57.2 mL/year [95% CI -3.5, 118.0]) than ATA-positive (difference: 29.9 mL/year [95% CI -19.1, 78.8]), but the exploratory interaction *P* value did not indicate heterogeneity in the difference between nintedanib and placebo between the subgroups (*P*=0.49) (Figure 1A).

The proportion of patients with an absolute decrease in FVC of ≥3.3% predicted at week 52 was lower with nintedanib than placebo both among patients who were ATA-positive (35.8% vs 45.8%) and ATA-negative (32.5% vs 40.5%); the exploratory interaction *P* value did not indicate heterogeneity in the difference between nintedanib and placebo between the subgroups (*P* =0.86). The proportion of patients with an increase or absolute decrease in FVC <3.3% predicted was higher with nintedanib than placebo both among patients who were ATA-positive (64.2% vs 54.2%) and ATA-negative (67.5% vs 59.5%) (exploratory interaction *P* =0.86) (Table 1).

Small reductions (improvements) in the mRSS were observed both in patients who were ATA-positive and ATA-negative. Reductions in the mRSS were similar in the nintedanib and placebo groups, with no heterogeneity detected in the between-group difference between the subgroups by ATA status (Table 1).

Outcomes in subgroups by mRSS at baseline

The adjusted annual rate (SE) of decline in FVC in the placebo group was greater in patients who had an mRSS ≥18 than <18 at baseline (-131.7 [29.2] mL/year vs -81.4

[15.4] mL/year) (Figure 1B, Table 2). The effect of nintedanib vs placebo on reducing the annual rate of decline in FVC was numerically more pronounced in patients who had an mRSS ≥18 at baseline (difference: 88.7 mL/year [95% CI 7.7, 169.8]) than an mRSS <18 at baseline (difference: 26.4 mL/year [95% CI -16.8, 69.6]), but the exploratory interaction *P* value did not indicate heterogeneity in the difference between nintedanib and placebo between the subgroups (*P* =0.18) (Figure 1B). Similarly, in analyses of subgroups by mRSS ≤10 (n=315), >10 to <22 (n=182) and ≥22 (n=76) at baseline, the exploratory interaction *P* value did not indicate heterogeneity in the treatment effect of nintedanib across the subgroups (*P*=0.07) (Supplementary Table 5).

The proportion of patients with an absolute decrease in FVC of ≥3.3% predicted was lower with nintedanib than placebo both among patients who had an mRSS ≥18 (42.0% vs 53.3%) and <18 at baseline (32.1% vs 40.7%). The proportion of patients with an increase or absolute decrease in FVC <3.3% predicted was higher with nintedanib than placebo both among patients who had an mRSS ≥18 (58.0% vs 46.7%) and <18 at baseline (67.9% vs 59.3%). Exploratory interaction *P* values did not indicate heterogeneity in the difference between nintedanib and placebo between the subgroups by mRSS at baseline (Table 2).

Small reductions (improvements) in the mRSS were observed both in patients with an mRSS ≥18 and <18 at baseline. Reductions in the mRSS were similar in the nintedanib and placebo groups, with no heterogeneity in treatment effect detected between the subgroups (Table 2). Similarly, there was no heterogeneity in the treatment effect of nintedanib across subgroups by mRSS ≤10, >10 to <22 and ≥22 at baseline (Supplementary Table 5).

Relationships between FVC and mRSS

In the overall population, no meaningful correlations were observed between FVC (mL) at baseline and change from baseline in mRSS at week 52, mRSS at baseline and change from baseline in FVC (mL) at week 52, or changes from baseline in mRSS and FVC (mL) at week 52 (Supplementary Table 6). The analysis that considered mRSS at baseline as a continuous variable showed no significant interaction between baseline mRSS and the rate of decline in FVC (mL/year) (*P*=0.12).

Outcomes in subgroups with lcSSc or dcSSc

The adjusted annual rate (SE) of FVC decline in patients who received placebo was greater in patients with dcSSc than lcSSc (-112.0 [19.1] mL/year versus -74.5 [19.2] mL/year). The effect of nintedanib versus placebo on reducing the annual rate of decline in FVC was numerically more pronounced in patients with dcSSc (difference: 56.6 mL/year [95% CI 3.2, 110.0]) than lcSSc (difference: 25.3 mL/year [95% CI -28.9, 79.6]), but the exploratory interaction *P* value did not indicate heterogeneity in the difference between nintedanib and placebo between these subgroups (*P* = 0.42). Small reductions (improvements) in the mRSS were observed both in patients with lcSSc and dcSSc. Reductions in the mRSS were similar in the nintedanib and placebo groups, with no heterogeneity in the between-group difference detected between subgroups (Supplementary Table 7).

DISCUSSION

We used data from the SENSCIS trial to assess the progression of ILD and skin fibrosis, and the effects of nintedanib versus placebo, in subgroups of patients with SSc-ILD based on baseline characteristics that have previously been associated with

disease progression. In the placebo group, the rate of decline in FVC over 52 weeks was similar between patients who were ATA-positive and ATA-negative, and greater in patients who had an mRSS ≥18 vs <18 at baseline and who had dcSSc vs lcSSc, as reported by the site investigator. A lower annual rate of decline in FVC was observed in patients treated with nintedanib versus placebo across these subgroups, with no heterogeneity detected in the effect of nintedanib versus placebo in any of the subgroups studied. These results add to previous analyses showing that the effect of nintedanib on the annual rate of FVC decline in the SENSCIS trial was consistent across subgroups defined by ATA status, lcSSc vs dcSSc, age, sex, race, and use of mycophenolate at baseline (19, 25). MCIDs for improvement in FVC and worsening of FVC in patients with SSc-ILD have been proposed based on data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36 (24). Across the subgroups by ATA status, mRSS at baseline and SSc subtype, over 52 weeks, the proportion of patients who met the proposed MCID threshold for improved or stable of FVC was numerically greater, and the proportion who met the proposed MCID threshold for worsening of FVC was numerically lower, in patients treated with nintedanib than placebo, with no evidence of heterogeneity across subgroups detected. These findings support a clinically meaningful benefit of nintedanib in reducing the rate of ILD progression across a broad population of patients with SSc-ILD.

In the placebo group, we observed a numerically greater rate of decline in FVC over 52 weeks in subjects with dcSSc than lcSSc. A single-center study of 105 patients with early SSc found that dcSSc was a predictor of decline in FVC ≥10% predicted over a mean follow-up of 6 years (26). However, in the GENISOS cohort of 266 patients with early SSc, decline in FVC % predicted over a mean follow-up of 3.8

years was similar between patients with lcSSc and dcSSc (16). A recent analysis of over 12,000 patients in the EUSTAR database also found that changes in FVC % predicted over 1, 2 and 3 years were similar between patients with lcSSc and dcSSc (27). In our analyses, among patients classified as having lcSSc, 51% were ATA-positive at baseline. This is a much higher proportion than has been reported in data from large registries of patients with SSc (11%–23%) (28-30). This may reflect misclassification of some patients who had dcSSc and whose skin fibrosis had regressed prior to screening, or selection bias in the SENSCIS trial for patients with lcSSc who had more progressive lung disease. These findings highlight the limitations of using the dcSSc versus lcSSc classification in large multi-centre trials. While data from the GENISOS cohort suggested that ATA positivity was associated with an increased rate of FVC decline in patients with early SSc (16), ATA status did not seem to affect the rate of ILD progression in the SENSCIS trial. These different findings across studies may reflect patient populations at different stages of disease or confounders such as comedication use.

Consistent with findings in the overall SENSCIS population (19), no effect of nintedanib on change in the mRSS was observed in any of the subgroups analyzed. The mRSS improved in both the nintedanib and placebo groups, reflecting the natural history of skin fibrosis in patients with SSc (10). In our analysis in subgroups by mRSS at baseline using a threshold of 18 (based on data suggesting an mRSS of 18–25 as an upper threshold to enrich a cohort of patients with dcSSc for skin-progressive patients (11)), change in mRSS at week 52 was similar between patients with mRSS ≥18 and <18 at baseline.

Among all the subgroups we analysed, the rate of decline in FVC over 52 weeks in the placebo group was greatest in patients who had an mRSS ≥18 at baseline;

however, we found no meaningful correlation between mRSS at baseline and decline in FVC over 52 weeks. We observed no meaningful correlation between progression of skin fibrosis over 52 weeks and progression of SSc-ILD over the same period. The relationship between progression of skin fibrosis and later decline in FVC observed over several years of follow-up in patients with dcSSc in the EUSTAR database (31) could not be investigated using data from the SENSCIS trial due to the limited follow-up period.

A limitation of the subgroup analyses of the SENSCIS trial is that they were not powered for formal statistical testing of the individual subgroups and the interaction *P* values should be regarded as exploratory. The results of these subgroup analyses should be interpreted with caution, particularly those in the relatively small subgroups. A further limitation was that progression of ILD was assessed solely by looking at changes in FVC and did not consider other metrics for ILD progression, such as changes in the extent of fibrosis on HRCT.

In conclusion, these analyses of data from the SENSCIS trial suggest that while the course of FVC decline in patients with SSc-ILD remains difficult to predict, nintedanib is effective at reducing the annual rate of ILD progression across subgroups of patients based on ATA status, SSc sub-type, and mRSS at baseline.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

Study conception and design: Masataka Kuwana, Maureen D Mayes, Martina Gahlemann, Margarida Alves, Oliver Distler

Acquisition of data: Masataka Kuwana, Yannick Allanore, Christopher P Denton, Jörg HW Distler, Virginia Steen, Dinesh Khanna, Maureen D Mayes, Oliver Distler

Analysis and interpretation of data: Masataka Kuwana, Yannick Allanore, Christopher P Denton, Jörg HW Distler, Virginia Steen, Dinesh Khanna, Marco Matucci-Cerinic, Maureen D Mayes, Elizabeth R Volkmann, Corinna Miede, Martina Gahlemann, Manuel Quaresma, Margarida Alves, Oliver Distler

ROLE OF THE STUDY SPONSOR

The sponsor participated in the study design, data collection, statistical analyses, data interpretation, and the writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

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Table 1. 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 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)**
Annual rate of decline in FVC (mL/year)*				
Rate of decline in FVC (mL/year) over 52 weeks, adjusted rate (SE)	-63.6 (18.0)	-93.5 (17.3)	-35.9 (21.8)	-93.1 (21.9)
Adjusted difference vs placebo (95% CI)	29.9 (-19.1, 78.8)		57.2 (-3.5, 118.0)	
P value for treatment-by-time-by-subgroup interaction	0.49			
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. (%)	62 (35.8)	81 (45.8)	37 (32.5)	45 (40.5)

Odds ratio vs placebo (95% CI)	0.66 (0.43, 1.02)		0.70 (0.41 ,1.22)	
P value for treatment-by-subgroup interaction	0.86			
Increase in FVC or decrease in FVC <3.3% predicted, no. (%)	111 (64.2)	96 (54.2)	77 (67.5)	66 (59.5)
Odds ratio vs placebo (95% CI)	1.51 (0.98, 2.32)		1.42 (0.82, 2.45)	
P value for treatment-by-subgroup interaction	0.86			
Change from baseline in mRSS at week 52§				
Change in mRSS at week 52, adjusted mean (SE)	-1.5 (0.3)	-1.7 (0.3)	-3.2 (0.4)	-2.4 (0.4)
Adjusted difference vs placebo (95% CI)	0.2 (-0.7, 1.2)		-0.8 (-2.0, 0.4)	
P value for treatment-by-visit-by-subgroup interaction	0.18			

*Post-baseline FVC data were not available for one ATA-negative patient 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 (23). [§]Baseline mRSS data were not available for two ATA-positive patients in the placebo group; these patients were excluded from the analysis. ATA = anti-topoisomerase I antibody; FVC = forced vital capacity; mRSS = modified Rodnan skin score.

Table 2. 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 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)**
Annual rate of decline in FVC (mL/year)*				
Rate of decline in FVC (mL/year) over 52 weeks, adjusted rate (SE)	-55.0 (15.7)	-81.4 (15.4)	-43.0 (29.2)	-131.7 (29.2)
Adjusted difference vs placebo (95% CI)	26.4 (-16.8, 69.6)		88.7 (7.7, 169.8)	
P value for treatment-by-time-by-subgroup interaction	0.18			
Proportions of patients who met proposed thresholds for worsening of FVC or stable or improved FVC† at week 52*				

Decrease in FVC ≥3.3% predicted, no. (%)	70 (32.1)	92 (40.7)	29 (42.0)	32 (53.3)
Odds ratio vs placebo (95% CI)	0.69 (0.47, 1.02)		0.62 (0.31, 1.25)	
P value for treatment-by-subgroup interaction	0.79			
Increase in FVC or decrease in FVC <3.3% predicted, no. (%)	148 (67.9)	134 (59.3)	40 (58.0)	28 (46.7)
Odds ratio vs placebo (95% CI)	1.44 (0.98, 2.13)		1.61 (0.80, 3.24)	
P value for treatment-by-subgroup interaction	0.79			
Change from baseline in mRSS at week 52				
Change in mRSS at week 52, adjusted mean (SE)	-2.2 (0.3)	-2.1 (0.3)	-2.1 (0.7)	-1.6 (0.7)
Adjusted difference vs placebo (95% CI)	-0.1 (-1.0, 0.7)		-0.6 (-2.1, 1.0)	
P value for treatment-by-visit-by-subgroup interaction	0.62			

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 <18 at baseline in the nintedanib group and 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 (23). FVC = forced vital capacity; mRSS = modified Rodnan skin score.

FIGURE LEGEND

Figure 1. Adjusted annual rate of decline in FVC (mL/year) in subgroups by ATA status at baseline (A) and mRSS at baseline (B) in the SENSCIS trial.