

Effect of Nintedanib on Progression of Systemic Sclerosis-Associated Interstitial Lung Disease Over 100 Weeks: Data From a Randomized Controlled Trial

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on behalf of the SENSICIS trial investigators

Objective. In the SENSICIS trial, participants with systemic sclerosis-associated interstitial lung disease (SSc-ILD) were randomized to receive nintedanib or placebo until the last participant reached week 52 but for 100 weeks or less. Nintedanib reduced the rate of decline in forced vital capacity (FVC) (ml/year) over 52 weeks by 44% (41 ml [95% confidence interval (95% CI): 2.9-79.0]) versus placebo. We investigated the effect of nintedanib over the whole SENSICIS trial.

Methods. The annual rate of decline in FVC (ml/year) over the whole trial was assessed descriptively using 1) on-treatment data plus off-treatment data from participants who prematurely discontinued treatment (intent-to-treat analysis) and 2) only on-treatment data to assess the effect of nintedanib in participants who remained on treatment.

Results. In the intent-to-treat analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was -54.9 (11.1) and -88.8 (10.9) ml/year in the nintedanib (n = 287) and placebo (n = 288) groups, respectively (difference 34.0 ml/year [95% CI: 3.4-64.5]). In the on-treatment analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was -55.1 (12.3) and -94.0 (11.7) ml/year in the nintedanib (n = 286) and placebo (n = 288) groups, respectively (difference 38.9 ml/year [95% CI: 5.6-72.1]). The adverse event profile of nintedanib over 100 weeks was consistent with that observed over 52 weeks.

Conclusion. Nintedanib provides a sustained benefit on slowing the progression of SSc-ILD over 100 weeks, with adverse events that are manageable for most patients.

INTRODUCTION

Systemic sclerosis (SSc) is a rare and clinically heterogeneous autoimmune disease characterized by fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common manifestation of SSc (2) and the leading cause of SSc-related death (3). Decline in forced vital capacity (FVC) in patients with SSc-ILD is indicative of disease progression and is associated with mortality (4–6). While there is no established definition of progression of SSc-ILD, in two recent Delphi consensus studies, physicians experienced in managing patients with SSc-ILD

agreed that measurement of lung function is an effective tool for assessing progression of ILD over the long term (7,8). Furthermore, it has been proposed that a decline in FVC of 10% or more, or a decline in FVC of 5% to 9% with a decline in diffusing capacity of the lungs for carbon monoxide (DLco) of 15% or more, over 1 to 2 years represents ILD progression (9,10).

Nintedanib is a tyrosine kinase inhibitor that inhibits processes fundamental to the progression of lung fibrosis (11,12). Nintedanib has been approved for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD in many countries. In the SENSICIS

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trial, participants with SSc-ILD were randomized to receive nintedanib or placebo until the last participant reached week 52 but for no longer than 100 weeks. The primary analysis showed that nintedanib reduced the rate of decline in FVC over 52 weeks by 44% versus placebo (-52.4 vs -93.3 ml/year; difference of 41.0 ml/year [95% confidence interval (95% CI): 2.9-79.0]), with no significant difference between groups in change in modified Rodnan skin score (mRSS), and a safety profile characterized predominantly by gastrointestinal adverse events (13,14). Additional analyses investigating the proportions of patients with categorical declines in FVC of greater than 5% and greater than 10% predicted over 52 weeks supported a benefit of nintedanib on slowing the progression of SSc-ILD (15). Here, we investigated the efficacy and safety of nintedanib over the whole SENSICIS trial (up to 100 weeks of treatment).

MATERIALS AND METHODS

Participants. The design of the SENSICIS trial has been published and the trial protocol is publicly available (13). Briefly, eligible participants had SSc and met the following criteria: their first non-Raynaud symptom occurred 7 years or less before screening, the extent of their fibrotic ILD was 10% or more on a high-resolution computed tomography scan, their FVC was 40% or more predicted, and their DLco was 30% to 89% predicted. Participants receiving prednisone at 10 mg/day or less or equivalent and/or stable therapy with mycophenolate or methotrexate for 6 months or more prior to randomization were allowed to participate.

Trial design. Participants were randomized 1:1 to receive nintedanib 150 mg twice a day or placebo, stratified by the presence of anti-topoisomerase I antibody (ATA). The trial was designed to demonstrate a reduction in the rate of decline in FVC (ml/year) in participants treated with nintedanib versus placebo over 52 weeks. Participants could remain on randomized blinded treatment until the last participant reached week 52 but for 100 weeks or less, resulting in a variable length of follow-up depending on when the participant was randomized. A post-treatment follow-up visit, at which FVC and adverse event data were collected, was conducted 28 days after the end of treatment. Participants who stopped treatment prematurely were asked to stay in the trial and attend visits up to 100 weeks or until the end of the trial. FVC was measured at baseline and at weeks 2, 4, 6, 12, 24, 36, 52, 68, 84, and 100. Spirometers were supplied by the sponsor. Measurements were performed by a qualified technician and readings were confirmed centrally in accordance with American Thoracic Society/European Respiratory Society guidelines (16). The trial was conducted in accordance with the protocol, the principles of the Declaration of Helsinki, and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and was approved by local authorities. All participants provided written informed consent.

Analyses. As for the primary analysis on data over 52 weeks, the annual rate of decline in FVC over the whole trial was analyzed using random coefficient regression, with fixed effects for treatment, ATA status, sex, baseline FVC (ml), age and height, and treatment-by-time and baseline-by-time interactions and a random effect for participant-specific intercept and time. Given the variable length of follow-up beyond week 52, two analytical approaches were of particular interest. The first followed an intent-to-treat approach to estimate the treatment effect regardless of premature treatment discontinuation (Supplementary Figure 1A). This analysis included on-treatment data plus off-treatment data from participants who prematurely discontinued treatment; post-treatment data from participants who completed the planned treatment period and discontinued treatment as per the trial design (ie, when the last participant reached week 52 or when they reached week 100) were not included. The second analysis included only on-treatment data to assess the expected effect of nintedanib in participants who remained on treatment. A pre-specified analysis, which aimed to reflect an intent-to-treat approach, was also performed based on all available data, including data collected after treatment discontinuation. However, because this analysis included data from the post-treatment follow-up visit from participants who had completed treatment as planned and only came off treatment at the end of the trial (as per the protocol) (Supplementary Figure 1A), this analysis does not represent an intent-to-treat approach; in practice, these patients would have continued treatment. For transparency, this analysis is presented in the Supplementary Material (Supplementary Figure 2B). Adjusted absolute changes from baseline in FVC over 100 weeks were analyzed using a mixed model for repeated measures, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction, age, sex, and height.

Time to absolute declines in FVC of greater than 5% predicted and greater than 10% predicted over 100 weeks and time to relative declines in FVC (ml) of greater than 5% and greater than 10% over 100 weeks were assessed using the intent-to-treat approach and using on-treatment data plus 1 day. Time to absolute decline in FVC of greater than 5% predicted and greater than 10% predicted over 100 weeks were assessed post-hoc using a Cox's regression model with terms for treatment and baseline FVC percentage predicted, stratified by ATA status. Time to relative decline in FVC (ml) of greater than 5% and greater than 10% over 100 weeks were assessed post-hoc using a Cox's regression model with terms for treatment, sex, baseline FVC (ml), age, and height, stratified by ATA status. Percentage predicted values for FVC were calculated using the Global Lung Initiative equations based on the participant's age, sex, race, and height (17).

Analyses of the annual rate of decline in FVC over 100 weeks, times to absolute decline in FVC of greater than 5% predicted and greater than 10% predicted over 100 weeks, and times to relative decline in FVC (ml) of greater

than 5% and greater than 10% over 100 weeks were repeated in subgroups by mycophenolate use at baseline. Analyses of the annual rate of decline in FVC over 100 weeks were repeated in subgroups by ATA status, sex, and SSc subtype (limited cutaneous SSc vs diffuse cutaneous SSc). Treatment-by-subgroup and treatment-by-subgroup-by-time, and subgroup and treatment-by-subgroup, were included as interaction terms in the random coefficient regression and Cox's regression models, respectively.

Adjusted absolute changes from baseline in mRSS at week 100 were analyzed using a mixed model for repeated measures, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction, and baseline-by-visit interaction. Time to absolute increase (worsening) from baseline in mRSS of 5 points or more was analyzed using a Cox's regression model with terms for treatment and baseline mRSS, stratified by ATA status.

Safety was assessed based on adverse events, reported irrespective of causality, from the first intake of the trial drug to the last intake plus 28 days. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities version 21.1. Adverse events are presented descriptively in the overall population and in subgroups based on age, sex, race, weight, ATA status, and mycophenolate use at baseline. Incidence rates of adverse events were calculated as the number of participants with the event divided by the time at risk and expressed per 100 patient-years.

RESULTS

Participants. A total of 576 participants received one or more dose(s) of trial drug. At baseline, mean (SD) FVC was 2500 (777) ml and 72.5 (16.7) % predicted, and 279 participants (48.4%) were taking mycophenolate. Over the whole trial, 74 participants (25.7%) in the nintedanib group and 46 participants

(16.0%) in the placebo group prematurely discontinued trial drug. The most common reason was adverse events: 53 (18.4%) and 33 (11.5%) participants treated with nintedanib and placebo, respectively, prematurely discontinued trial drug because of adverse events. In the nintedanib and placebo groups, respectively, 239 (83.0%) and 252 (87.5%) participants completed the treatment period and follow-up visit or prematurely discontinued trial drug but attended further visits as planned (Figure 1). Of those treated, 73 participants (25.3%) in the nintedanib group and 73 participants (25.3%) in the placebo group provided an FVC value at week 100. Median exposure to trial drug was 15.4 months in the nintedanib group and 15.6 months in the placebo group. Maximum exposure in these groups, respectively, was 23.2 and 23.8 months.

Decline in FVC. In the intent-to-treat analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was -54.9 (11.1) ml/year in the nintedanib group and -88.8 (10.9) ml/year in the placebo group (difference of 34.0 ml/year [95% CI: 3.4-64.5]); the estimated between-group difference in FVC at week 100 was 65.3 ml (Figure 2).

In the on-treatment analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was -55.1 (12.3) ml/year in the nintedanib group and -94.0 (11.7) ml/year in the placebo group (difference of 38.9 ml/year [95% CI: 5.6-72.1]); the estimated between-group difference in FVC at week 100 was 74.7 ml (Figure 2). Curves depicting the adjusted absolute changes from baseline in FVC (ml) over 100 weeks are presented in Figure 3.

The risks of experiencing an absolute decline in FVC of greater than 5% or greater than 10% predicted, or a relative decline in FVC (ml) of greater than 5% and greater than 10%, over 100 weeks were numerically lower in the nintedanib group than in the placebo group (Table 1).

Results of the subgroup analyses by mycophenolate use at baseline are presented in Table 2 and Supplementary Figure 3.

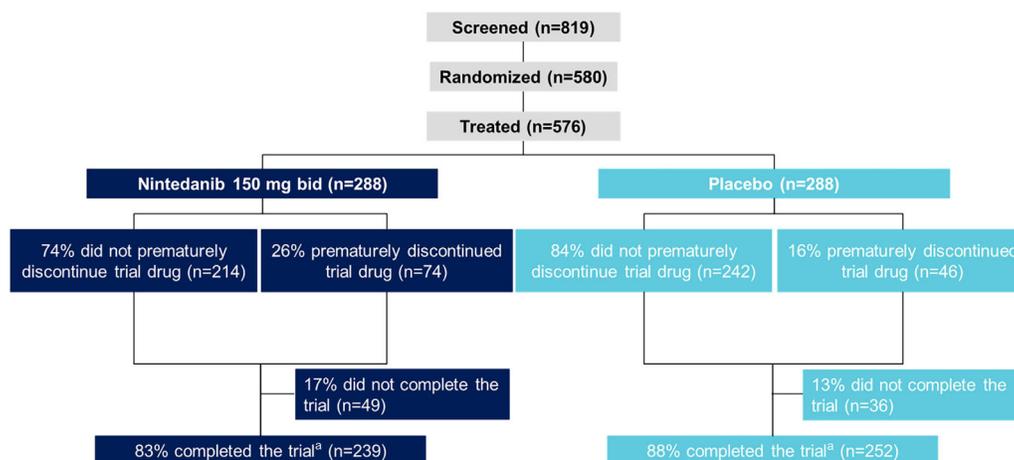


Figure 1. Disposition of participants over the SENSICIS trial. ^aCompleted treatment period (and follow-up visit) according to the protocol or prematurely discontinued trial drug but attended further visits as planned.

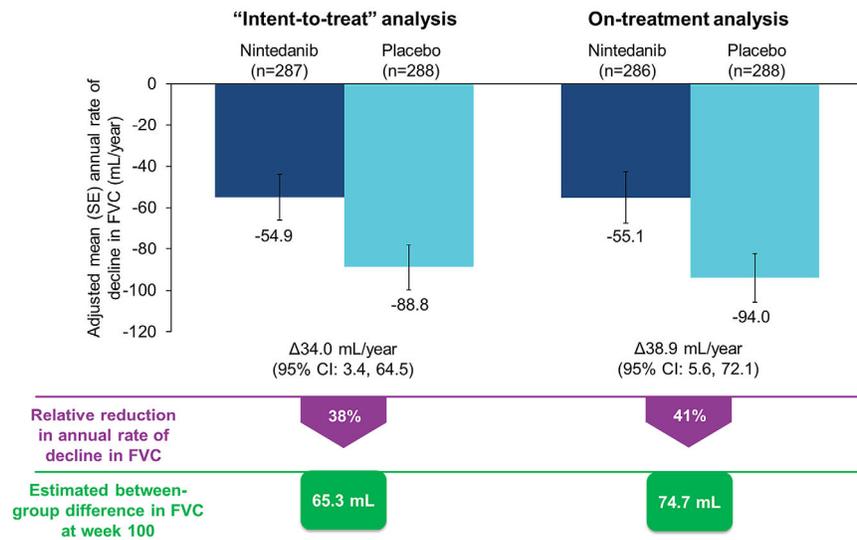


Figure 2. Annual rate of decline in FVC (mL/year) over 100 weeks. CI, confidence interval; FVC, forced vital capacity.

In both the intent-to-treat and on-treatment analyses, the effect of nintedanib on the annual rate of decline in FVC over 100 weeks was numerically smaller in participants who were taking mycophenolate at baseline than in those who were not (Table 2). The exploratory interaction *P* values for heterogeneity in the effect of nintedanib on the annual rate of FVC decline between the subgroups were *P* = 0.072 in the intent-to-treat analysis and *P* = 0.45 in the on-treatment analysis. The risks of experiencing an absolute decline in FVC of greater than 5% or greater than 10% predicted, or a relative decline in FVC (ml) of greater than 5% and greater than 10%, over 100 weeks were numerically lower in the nintedanib group than in the placebo group in both subgroups by mycophenolate use (Supplementary Figure 3). The exploratory interaction *P* values for heterogeneity in the effect

of nintedanib ranged from *P* = 0.21 to *P* = 0.56. The treatment effect of nintedanib between subgroups by mycophenolate use at baseline showed some variability across the FVC-based end points; however, considering all the analyses and the widely overlapping CIs, the results did not indicate a heterogeneous effect of nintedanib between these subgroups. The adjusted mean annual rates of decline in FVC over 100 weeks in subgroups by ATA status, sex, and SSc subtype, based on the intent-to-treat analysis, are presented in Supplementary Tables 1 to 3. The exploratory interaction *P* values did not indicate a heterogeneous effect of nintedanib across these subgroups.

Changes in mRSS. Small reductions (improvements) in mRSS were observed in both treatment groups. A numerically

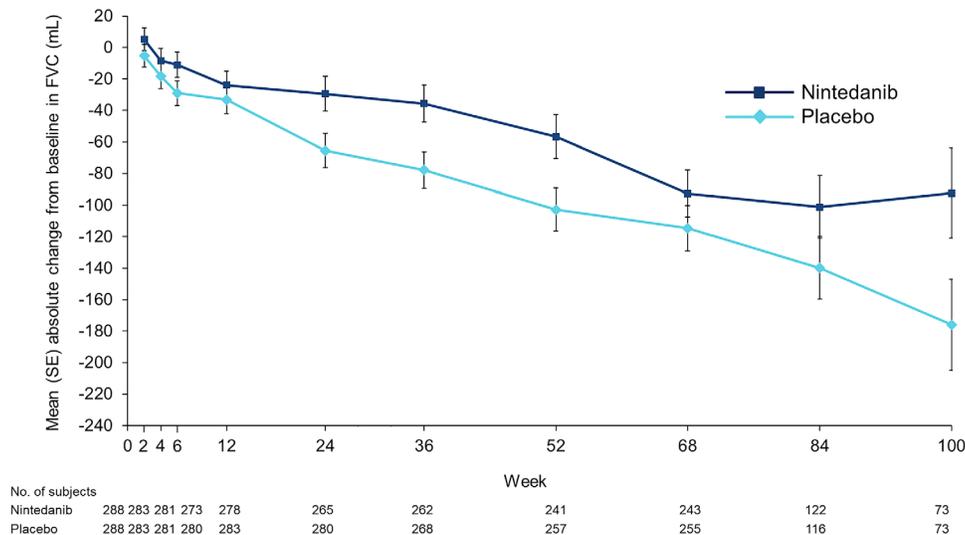


Figure 3. Adjusted absolute changes from baseline in FVC over 100 weeks. FVC, forced vital capacity.

Table 1. Absolute and relative declines in FVC over 100 weeks (assessed as time to event)

	Nintedanib (n = 288)	Placebo (n = 288)
Intent-to-treat analysis		
Absolute decline in FVC >5% predicted, n (%)	130 (45.1)	150 (52.1)
HR (95% CI)	0.83 (0.66-1.05)	
P value	0.12	
Absolute decline in FVC >10% predicted, n (%)	52 (18.1)	67 (23.3)
HR (95% CI)	0.79 (0.55-1.13)	
P value	0.19	
Relative decline in FVC (ml) >5%, n (%)	171 (59.4)	201 (69.8)
HR (95% CI)	0.80 (0.65-0.99)	
P value	0.04	
Relative decline in FVC (ml) >10%, n (%)	103 (35.8)	117 (40.6)
HR (95% CI)	0.88 (0.67-1.14)	
P value	0.33	
On-treatment analysis		
Absolute decline in FVC >5% predicted, n (%)	117 (40.6)	144 (50.0)
HR (95% CI)	0.80 (0.63-1.02)	
P value	0.07	
Absolute decline in FVC >10% predicted, n (%)	46 (16.0)	65 (22.6)
HR (95% CI)	0.75 (0.51-1.09)	
P value	0.13	
Relative decline in FVC (ml) >5%, n (%)	156 (54.2)	194 (67.4)
HR (95% CI)	0.78 (0.63-0.96)	
P value	0.02	
Relative decline in FVC (ml) >10%, n (%)	91 (31.6)	113 (39.2)
HR (95% CI)	0.82 (0.62-1.09)	
P value	0.17	

Abbreviations: CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio.

smaller proportion of participants treated with nintedanib than a placebo experienced an increase from baseline in mRSS of 5 points or more over 100 weeks (13.9% vs 16.7%) (Supplementary Table 4).

Adverse events. The most frequent adverse event over up to 100 weeks of treatment was diarrhea, which was reported in

76.4% of participants treated with nintedanib and 32.6% of participants who received a placebo; 7.6% and 0.3% of participants in the nintedanib and placebo groups, respectively, permanently discontinued trial drug because of diarrhea (Table 3). Serious adverse events were reported in 30.6% of participants treated with nintedanib and 27.4% of participants treated with placebo; fatal adverse events were reported in 2.1% and 1.7% of participants in the nintedanib and placebo groups, respectively. Elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels of three or more times the upper limit of normal (ULN) were reported in 5.6% of participants in the nintedanib group and 0.7% of participants in the placebo group. No participants met criteria for Hy's law (ALT and/or AST level greater than or equal to three times the ULN and bilirubin level greater than or equal to two times the ULN). The proportions of participants with major adverse cardiovascular events, myocardial infarction, and bleeding adverse events are shown in Supplementary Table 5. Major adverse cardiovascular events were reported in a smaller proportion of participants treated with nintedanib than placebo. No participants treated with nintedanib had a myocardial infarction. Bleeding adverse events were balanced between treatment groups.

The adverse event profile of nintedanib over up to 100 weeks of treatment was generally consistent across subgroups based on age, sex, race, weight, ATA status, and mycophenolate use at baseline (Supplementary Tables 6-11).

DISCUSSION

We evaluated the efficacy and safety of nintedanib in participants with SSc-ILD over the whole SENSICIS trial. Our results, based on data from up to 100 weeks of treatment, suggested that the effect of nintedanib on slowing the progression of SSc-ILD observed over the first 52 weeks persisted beyond that period. The annual rate of decline in FVC over 100 weeks was lower in participants treated with nintedanib than in those treated with placebo across all the analytical methods used. In the analysis that used an intent-to-treat approach, which we consider to be the most relevant, nintedanib reduced the annual

Table 2. Annual rate of decline in FVC (ml/year) over 100 weeks in subgroups by mycophenolate use at baseline

	Participants taking mycophenolate at baseline		Participants not taking mycophenolate at baseline	
	Nintedanib	Placebo	Nintedanib	Placebo
Intent-to-treat analysis, n				
Adjusted mean (SE) annual rate of decline in FVC (ml/year)	138	140	149	148
Difference (95% CI)	-54.4 (15.7) -59.8 (15.5)		-55.1 (15.6) -116.4 (15.2)	
Treatment-by-time-by-subgroup interaction P value	5.4 (-37.9 to 48.8)		61.3 (18.6 to 104.0)	
0.072				
On-treatment analysis, n				
Adjusted mean (SE) annual rate of decline in FVC (ml/year)	138	140	148	148
Difference (95% CI)	-45.0 (17.2) -70.7 (16.6)		-65.2 (17.4) -116.3 (16.3)	
Treatment-by-time-by-subgroup interaction P value	25.7 (-21.3 to 72.7)		51.1 (4.3 to 98.0)	
0.45				

Abbreviations: CI, confidence interval; FVC, forced vital capacity.

Table 3. Adverse events

	Nintedanib (n = 288)		Placebo (n = 288)	
	n (%)	Incidence rate (per 100 patient- years)	n (%)	Incidence rate (per 100 patient- years)
Any adverse event(s)	283 (98.3)	1156.1	281 (97.6)	456.3
Most frequent adverse events ^a				
Diarrhea	220 (76.4)	201.7	94 (32.6)	32.5
Nausea	96 (33.3)	35.9	41 (14.2)	11.6
Vomiting	78 (27.1)	26.9	33 (11.5)	8.9
Skin ulcer	57 (19.8)	18.2	56 (19.4)	16.0
Nasopharyngitis	43 (14.9)	13.0	56 (19.4)	15.9
Cough	41 (14.2)	12.1	63 (21.9)	18.5
Upper respiratory tract infection	39 (13.5)	11.5	44 (15.3)	12.2
Weight decreased	39 (13.5)	11.5	15 (5.2)	3.9
Abdominal pain	36 (12.5)	10.6	21 (7.3)	5.6
Headache	34 (11.8)	10.0	28 (9.7)	7.5
Fatigue	33 (11.5)	9.8	21 (7.3)	5.6
Urinary tract infection	29 (10.1)	8.4	28 (9.7)	7.5
Dyspnea	27 (9.4)	7.7	31 (10.8)	8.2
Severe adverse event(s) ^b	62 (21.5)	18.8	44 (15.3)	11.7
Adverse event(s) leading to permanent discontinuation of trial drug	50 (17.4)	13.9	29 (10.1)	7.3
Most frequent adverse events leading to permanent discontinuation of trial drug ^c				
Diarrhea	22 (7.6)	6.0	1 (0.3)	0.3
Nausea	6 (2.1)	1.6	0	0
Vomiting	4 (1.4)	1.1	1 (0.3)	0.3

Note: Data are n (%) of participants with ≥ 1 such adverse event.

^aAdverse events reported in $>10\%$ of participants in either treatment group are shown, coded according to preferred terms in the Medical Dictionary for Regulatory Activities.

^bEvents that were incapacitating or that caused an inability to work or to perform usual activities.

^cAdverse events that led to permanent discontinuation in $>1\%$ of participants in either treatment group are shown.

rate of decline in FVC (ml/year) over 100 weeks by 38%, similar to the 44% relative reduction observed over 52 weeks (13). It would be expected that the relative reduction in the rate of FVC decline with nintedanib versus placebo observed over 100 weeks would be slightly lower than that observed over 52 weeks because more data from patients who prematurely discontinued nintedanib (and so lost the effect of treatment) are included. These results were supported by time-to-event analyses based on categorical declines in FVC and by applying standard censoring rules. Of note, our findings were obtained in a patient population of whom almost half were taking mycophenolate at baseline. The treatment effects of nintedanib on FVC end points showed some variability between the subgroups by mycophenolate use at baseline, and the effect on the annual rate of decline in FVC was numerically smaller in participants taking mycophenolate than in participants not taking mycophenolate.

It is interesting to note that 52% of participants in the placebo group experienced an absolute decline in FVC of greater than 5% predicted over 100 weeks, suggesting that although the inclusion criteria for the SENSICIS trial did not require that patients have recent evidence of ILD progression, and almost half were taking mycophenolate at baseline, the majority of

patients enrolled in the trial exhibited progressive ILD. Considering the age at onset of SSc, and the association between FVC decline and mortality in patients with SSc-ILD (4–6), the observed reduction in the rate of decline in FVC in participants who received nintedanib in the SENSICIS trial is clinically relevant. These data are supported by those of INPULSIS-ON, the long-term extension of the INPULSIS trials in participants with IPF, which suggested that the effect of nintedanib on slowing the rate of decline in FVC persisted beyond 4 years (18). An ongoing open-label extension of the SENSICIS trial, SENSICIS-ON (NCT03313180), will provide long-term data on the effects of nintedanib in patients with SSc-ILD.

The safety and tolerability profile of nintedanib observed over 100 weeks was consistent with that observed over 52 weeks (13,14) and with the profile established in patients with IPF and other chronic fibrosing ILDs (18–20). A comparison of the permanent treatment discontinuations that occurred over 100 weeks with those that occurred over 52 weeks (13) shows that only four patients discontinued nintedanib after 52 weeks of treatment, of whom two discontinued because of diarrhea. As observed over 52 weeks of treatment (21), although mycophenolate is also associated with gastrointestinal adverse events, permanent discontinuations of nintedanib over

100 weeks were not more frequent, compared with placebo, in participants taking concomitant mycophenolate than in participants taking nintedanib alone, supporting the tolerability of this combination.

Strengths of our analyses include the broad population of patients enrolled in the SENSICIS trial, the standardized collection and reading of FVC data, the high proportion of participants who completed the trial in both treatment groups, and the consistent results obtained using different statistical methods to investigate the effect of nintedanib on FVC decline. Given that the SENSICIS trial was designed to demonstrate a reduction in the rate of FVC decline over 52 weeks, our analyses also have limitations, including the post-hoc nature of the intent-to-treat and on-treatment analyses; missing FVC data, particularly, due to the trial design, at the later time points; and selection bias in the participants who continued longer in the trial. Thus, the analyses of the data beyond 52 weeks should be considered exploratory. We were unable to investigate changes in St. George's Respiratory Questionnaire (SGRQ) score over 100 weeks because after week 52, the SGRQ was only completed at the end of the treatment visit.

In conclusion, these analyses suggest that the effect of nintedanib on slowing the progression of SSc-ILD observed over 52 weeks persisted over the duration of the SENSICIS trial. The results of the SENSICIS trial suggest that nintedanib provides a sustained benefit on slowing the progression of SSc-ILD, with adverse events that are manageable for most patients.

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AUTHOR CONTRIBUTIONS

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 published. Dr. Voss had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

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REFERENCES

- van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737–47.
- Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. *Nat Rev Dis Primers* 2015;1:15002.
- Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017;76:1897–905.
- Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol* 2017;69:1670–8.
- Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med* 2019;200:1258–66.
- Volkman ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. *Ann Rheum Dis* 2019;78:122–30.
- Rahaghi FF, Streck ME, Southern BD, Saggari R, Hsu VM, Mayes MD, et al. Expert consensus on the screening, treatment, and management of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), and the potential future role of anti-fibrotic drugs in a treatment paradigm for SSc-ILD: a Delphi Consensus Study [poster]. Presented at the American Thoracic Society International Conference; 2019 May 17–22; Dallas, Texas.
- Hoffmann-Vold A, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020;2:e71–83.
- Khanna D, Mittoo S, Aggarwal R, Proudman SM, Dalbeth N, Matteson EL, et al. Connective tissue disease-associated interstitial lung diseases (CTD-ILD): report from OMERACT CTD-ILD Working Group. *J Rheumatol* 2015;42:2168–71.
- Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020;55:1902026.
- Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:1434–445.
- Wollin L, Distler JH, Denton CP, Gahlemann M. Rationale for the evaluation of nintedanib as a treatment for systemic sclerosis-associated interstitial lung disease. *J Scleroderma Relat Disord* 2019;4:212–8.
- Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019;380:2518–28.
- Seibold JR, Maher TM, Highland KB, Assassi S, Azuma A, Hummers LK, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSICIS trial. *Ann Rheum Dis* 2020;79:1478–84.
- Maher TM, Mayes MD, Kreuter M, Volkman ER, Aringer M, Castellvi I, et al. Effect of nintedanib on lung function in patients with systemic sclerosis-associated interstitial lung disease: further analyses of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2021;73:671–6.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.

18. Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. *Lancet Respir Med* 2019;7:60–8.
19. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
20. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SL, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–27.
21. Highland KB, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A, et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: subgroup analysis of the SENSICIS trial. *Lancet Respir Med* 2021;9:96–106.