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CLINICAL SCIENCE

Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON

Yannick Allanore ,[1] Madelon C Vonk ,[2] Oliver Distler ,[3] Arata Azuma,[4] Maureen D Mayes,[5] Martina Gahlemann,[6] Alexandra James,[7] Veronika Kohlbrenner,[8] Margarida Alves,[9] Dinesh Khanna ,[10] Kristin B Highland,[11] on behalf of the SENSCIS-ON trial investigators

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For numbered affiliations see end of article.

Correspondence to
Professor Yannick Allanore, Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France; yannick.allanore@me.com

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ABSTRACT

Objectives In the SENSCIS trial in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib reduced the rate of decline in forced vital capacity (FVC) versus placebo, with adverse events that were manageable for most patients. An open-label extension trial, SENSCIS-ON, is assessing safety and FVC decline during longer term nintedanib treatment.

Methods Patients who completed the SENSCIS trial or a drug–drug interaction (DDI) study of nintedanib and oral contraceptive on treatment were eligible to enter SENSCIS-ON. Adverse events and changes in FVC over 52 weeks of SENSCIS-ON were assessed in patients who received nintedanib in SENSCIS and continued nintedanib in SENSCIS-ON ('continued nintedanib' group) and in patients who received placebo in SENSCIS and initiated nintedanib in SENSCIS-ON or who received nintedanib for ≤28 days in the DDI study ('initiated nintedanib' group).

Results There were 197 patients in the continued nintedanib group and 247 in the initiated nintedanib group. Diarrhoea was reported in 68.0% and 68.8% of patients in these groups, respectively. Adverse events led to discontinuation of nintedanib in 4.6% and 21.5% of the continued nintedanib and initiated nintedanib groups, respectively. Mean (SE) changes in FVC from baseline to week 52 of SENSCIS-ON were −58.3 (15.5) mL in the continued nintedanib group and −44.0 (16.2) mL in the initiated nintedanib group.

Conclusions The safety profile of nintedanib over 52 weeks of SENSCIS-ON was consistent with that reported in SENSCIS. The change in FVC over 52 weeks of SENSCIS-ON was similar to that observed in the nintedanib group of SENSCIS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The results of the randomised placebo-controlled SENSCIS trial showed that in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib reduced the rate of decline in forced vital capacity (FVC) over 52 weeks.

WHAT THIS STUDY ADDS

⇒ The results of this open-label extension study show that the safety profile of nintedanib over longer term use was consistent with that seen in the SENSCIS trial and that the change in FVC over 52 weeks of the open-label extension was similar to that seen in patients who received nintedanib in SENSCIS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that nintedanib can be used over the long term to slow the progression of SSc-ILD and so improve patient outcomes.

INTRODUCTION

Systemic sclerosis is a heterogeneous autoimmune disease characterised by multiorgan vascular and fibrotic abnormalities.[1] Interstitial lung disease (ILD) is a common manifestation of SSc, which most frequently develops early in the disease course.[2] Systemic sclerosis-associated ILD (SSc-ILD) has a variable course and in some patients becomes progressive, characterised by an increase in fibrotic abnormalities on high-resolution CT (HRCT), a decline in forced vital capacity (FVC) and premature death.[3 4] A decline in FVC in patients with SSc-ILD is predictive of mortality.[3 5 6] There is no established algorithm to inform when pharmacotherapy for SSc-ILD should be initiated or which therapy should be used. Treatment decisions should be made on a case-by-case basis, taking into account the severity of ILD, risk factors for progression, other manifestations of SSc and the patient's preferences.[7 8]

Nintedanib, a tyrosine kinase inhibitor with anti-inflammatory and antifibrotic properties,[9] has been licensed for the treatment of SSc-ILD as well as for the treatment of idiopathic pulmonary fibrosis (IPF) and other chronic fibrosing ILDs with a progressive phenotype. The efficacy and safety of nintedanib in patients with SSc-ILD were investigated in the SENSCIS trial, in which patients were randomised to receive nintedanib or placebo until the last patient had reached week 52 but for a maximum of 100 weeks.[10] Over 52 weeks, nintedanib reduced the rate of decline in FVC (mL/year) by 44% compared with placebo, with an adverse event profile characterised predominantly by gastrointestinal events,

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particularly diarrhoea. Data collected over the whole SENSCIS trial (up to 100 weeks of treatment) suggested that nintedanib provided a sustained benefit on slowing the progression of SSc-ILD over 100 weeks, with adverse events that were manageable for most patients.[11] An open-label extension of SENSCIS, SENSCIS-ON, is assessing the safety and tolerability of nintedanib over the longer term. Exploratory data on FVC are also being collected. Here, we present data from the first year of SENSCIS-ON.

METHODS

Trial design

Patients in SENSCIS-ON (NCT03313180) came from two parent trials: SENSCIS (NCT02597933) and a drug–drug interaction (DDI) study (NCT03675581). SENSCIS enrolled patients with SSc-ILD with onset of first non-Raynaud symptom in the prior ≤7 years, extent of fibrotic ILD on HRCT ≥10% and FVC≥40% predicted.[10] Patients receiving prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months were allowed to participate. Patients were randomised to receive nintedanib 150 mg two times per day or placebo, stratified by antitopoisomerase I antibody status, until the last patient had reached week 52 but for ≤100 weeks. Patients who completed SENSCIS on treatment and attended a follow-up visit 28 days later were eligible to participate in SENSCIS-ON. Per protocol, the off-treatment period between SENSCIS and SENSCIS-ON was ≤12 weeks.

The DDI study from which patients could enter SENSCIS-ON was an open-label study of nintedanib plus oral contraceptive (Microgynon; ethinylestradiol and levonorgestrel) in female patients with SSc-ILD.[12] Patients receiving prednisone ≤10 mg/day or equivalent and/or stable therapy with methotrexate for ≥6 months were allowed to participate. Treatment with mycophenolate ≤2 weeks prior to the start of the study was not permitted. Patients received nintedanib 150 mg two times per day over a period of ≥14 days to approximately 28 days. Per protocol, the off-treatment period between this study and SENSCIS-ON was ≤7 days.

In both SENSCIS and the DDI study, dose reductions to 100 mg two times per day were permitted to manage adverse events and dose could be increased back to 150 mg two times per day once the adverse event had resolved. Treatment could be interrupted for ≤4 weeks or ≤8 weeks to manage adverse events considered to be related to study drug, or not related to study drug, respectively. Patients receiving nintedanib or placebo at a dose of 150 mg two times per day at the end of the parent study received nintedanib 150 mg two times per day in SENSCIS-ON. Patients receiving nintedanib or placebo at a dose of 100 mg two times per day at the end of the parent study could receive nintedanib 100 mg two times per day or 150 mg two times per day in SENSCIS-ON. In SENSCIS-ON, nintedanib dose reductions from 150 mg two times per day to 100 mg two times per day were permitted, and treatment could be interrupted for ≤4 weeks or ≤12 weeks to manage adverse events considered to be related to study drug, or not related to study drug, respectively. FVC was assessed at baseline and at weeks 4, 12, 24, 36 and 52, using sponsor-supplied spirometers, in accordance with American Thoracic Society/European Respiratory Society guidelines.[13] FVC measurements were centrally reviewed.

SENSCIS-ON is being carried out in compliance with the protocol and in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, applicable regulatory requirements and standard operating procedures. Patients provided written informed consent prior to entry into the trial.

Exclusion criteria

Patients with aspartate aminotransferase or alanine aminotransferase >3 times the upper limit of normal (ULN) or bilirubin >2 times the ULN were excluded from SENSCIS-ON, as were patients at risk of bleeding and patients with major thromboembolic events following completion of the parent trial. A complete list of the exclusion criteria is provided in the supplemental material.

Endpoints

Adverse events, reported irrespective of causality, with onset from the first drug intake to week 52 (or to the last drug intake plus 7 days for patients who prematurely discontinued treatment) were coded using the Medical Dictionary for Regulatory Activities V.22.1. Serious adverse events were defined as adverse events that resulted in death, were life threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect or were deemed serious for any other reason. Recommendations for the management of diarrhoea and liver enzyme elevations were provided to the investigators.[14] Efficacy endpoints assessed at week 52 included absolute change from baseline in FVC (mL); the proportions of patients with relative categorical increase and decline in FVC (mL); the cumulative distribution of patients by absolute change from baseline in FVC % predicted; and changes from baseline in the modified Rodnan skin score (mRSS), St. George's Respiratory Questionnaire (SGRQ) total score and University of California Los Angeles (UCLA) Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT) V.2.0 instrument total score. The mRSS measures skin thickness based on palpation of 17 areas, each rated on a scale of 0–3, with higher scores indicating worse skin thickening.[15] The SGRQ is a measure of health-related quality of life (HRQL) in patients with respiratory diseases and comprises three domains: impact, symptoms and activity.[16] Each domain score and the total score are scaled from 0 to 100, with higher scores indicating worse HRQL. The UCLA SCTC GIT instrument V.2.0 comprises seven scales measuring the severity and impact of gastrointestinal symptoms: reflux, distension or bloating, faecal soilage, diarrhoea, constipation, emotional well-being, social functioning.[17] Each scale is scored from 0 to 3 except for diarrhoea (0 to 2) and constipation (0 to 2.5). The total score, derived as the mean of the scores for the scales except constipation, ranges from 0 to 2.83, with higher scores indicating worse symptoms.

Analyses

Analyses were conducted in patients who had received nintedanib in SENSCIS and continued nintedanib in SENSCIS-ON ('continued nintedanib' group), and in patients who had received placebo in SENSCIS and initiated nintedanib in SENSCIS-ON or who had received nintedanib for a brief period in the DDI study ('initiated nintedanib' group). All analyses were descriptive and conducted in patients who received ≥1 dose of trial medication. Changes from baseline in each endpoint were based on observed data available at the respective time point. The cumulative distribution of patients by absolute change from baseline in FVC % predicted was determined *post hoc* based on the worst observation carried forward method. In *post hoc*

Table 1 Baseline characteristics of patients at inclusion in SENSCIS-ON

	Continued nintedanib (n=197)	Initiated nintedanib (n=247)
Female, n (%)	148 (75.1)	187 (75.7)
Age, years, mean (SD)	55.8 (11.3)	54.4 (12.3)
Weight, kg, mean (SD)	68.0 (15.2)	70.7 (16.6)
Body mass index, kg/m^2, mean (SD)	25.4 (4.6)	26.1 (5.2)
Race, n (%)		
White	142 (72.1)	166 (67.2)
Asian	42 (21.3)	68 (27.5)
Black or African-American	9 (4.6)	9 (3.6)
Other	4 (2.0)	4 (1.6)
FVC, mL, mean (SD)	2379 (754)	2443 (814)
FVC, % predicted, mean (SD)	70.4 (18.1)	70.8 (17.9)
mRSS, mean (SD)	8.5 (7.7)	8.8 (7.8)
SGRQ total score, mean (SD)	41.5 (20.6)	37.8 (21.9)
UCLA SCTC GIT total score, mean (SD)	0.33 (0.33)	0.33 (0.34)
Taking mycophenolate, n (%)	105 (53.3)	127 (51.4)

FVC, forced vital capacity; SGRQ, St. George's Respiratory Questionnaire; UCLA, University of California Los Angeles; UCLA SCTC GIT, UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract.

analyses, adverse events and absolute change from baseline in FVC (mL) at week 52 were analysed in subgroups by mycophenolate use at the start of SENSCIS-ON.

RESULTS

Patients

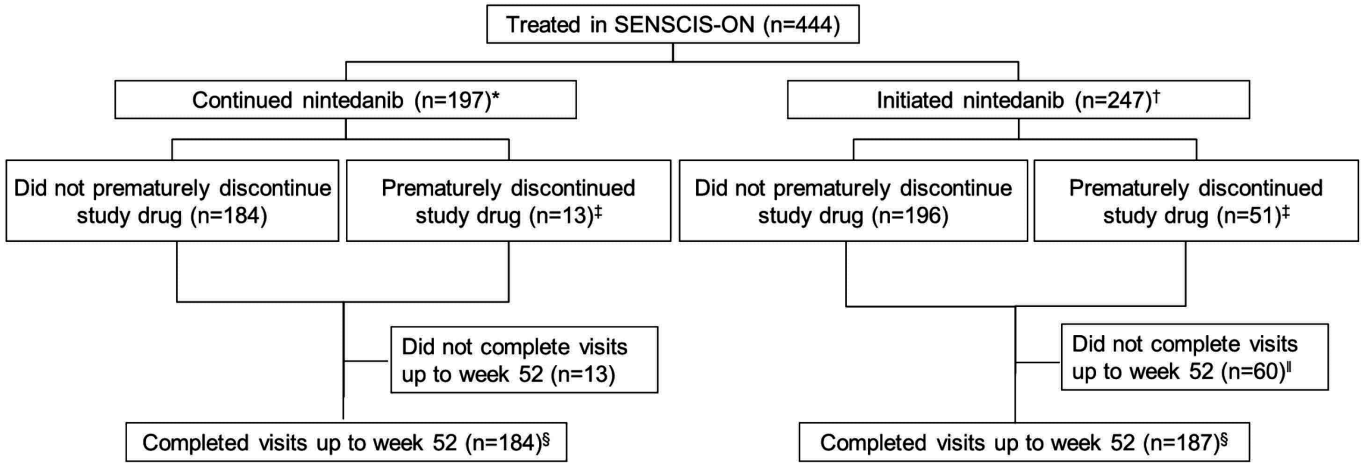
Of the 473 patients who completed SENSCIS (n=456) or the DDI study (n=17) on treatment, 444 (93.9%) entered SENSCIS-ON. There were 197 patients in the continued nintedanib group and 247 patients (231 from SENSCIS, 16 from the DDI study) in the initiated nintedanib group. Baseline characteristics at entry into SENSCIS-ON were generally similar between patients who continued and initiated nintedanib (table 1). The majority of patients were women (75.5%) and white (69.4%); mean (SD) FVC at baseline was 70.6 (18.0) % predicted; 232 patients (52.3%) were taking mycophenolate. Baseline characteristics at entry into SENSCIS-ON in subgroups by mycophenolate use are shown in online supplemental table S1. In the continued nintedanib and initiated nintedanib groups, respectively, 13 (6.6%) and 51 (20.6%) patients permanently discontinued nintedanib before week 52 (figure 1).

Exposure

Due to the trial design, the patients rolled over from SENSCIS into SENSCIS-ON had received different exposures to trial drug in SENSCIS (52–100 weeks). The median (minimum and maximum) off-treatment period between SENSCIS and SENSCIS-ON was 44 (26 and 88) days in patients who continued nintedanib in SENSCIS-ON and 49 (24 and 140) days in patients who initiated nintedanib in SENSCIS-ON. The median (minimum and maximum) off-treatment period between the DDI study and SENSCIS-ON was 8 (6 and 37) days. Median (minimum and maximum) exposure over 52 weeks in SENSCIS-ON was 13.8 (0.2, 13.8) months in the continued nintedanib group and 13.8 (0.0 and 13.8) months in the initiated nintedanib group. Total median (minimum and maximum) exposure to nintedanib across both SENSCIS and SENSCIS-ON was 29.5 (12.8 and 37.0) months. Among those in the continued nintedanib group, 54 patients (27.4%) had >36 months' exposure to nintedanib across both SENSCIS and SENSCIS-ON.

Adverse events and dose adjustments

Adverse events are shown in table 2. Diarrhoea was the most frequent adverse event, reported in 134 patients (68.0%) who continued nintedanib and 170 patients (68.8%) who initiated nintedanib. In the continued nintedanib and initiated nintedanib groups, respectively, the worst diarrhoea event was mild or moderate in intensity in 99.3% and 95.3% of the patients who had diarrhoea. Among patients who experienced diarrhoea, 3 (2.2%) and 17 (10.0%) patients who continued and initiated nintedanib, respectively, permanently discontinued nintedanib due to diarrhoea. Liver test



*Patients randomised to nintedanib in SENSCIS continued nintedanib in SENSCIS-ON.
†Patients from the drug–drug interaction study were pooled with patients randomised to placebo in SENSCIS.
‡Premature discontinuations recorded prior to the 52-week time window (i.e. up to day 310).
§Patients were considered as having completed visits up to week 52 if they had ≥1 visit during and/or after the 52-week time window (days 310–421).
‖11 patients had not reached this time point at the time of this interim analysis.

Figure 1 Disposition of patients in SENSCIS-ON.

Table 2 Adverse events (reported irrespective of causality) in SENSCIS and SENSCIS-ON

	SENSCIS		SENSCIS-ON	
	Nintedanib (n=288)	Placebo (n=288)	Continued nintedanib (n=197)	Initiated nintedanib (n=247)
Diarrhoea	218 (75.7)	91 (31.6)	134 (68.0)	170 (68.8)
Nausea	91 (31.6)	39 (13.5)	32 (16.2)	60 (24.3)
Vomiting	71 (24.7)	30 (10.4)	27 (13.7)	53 (21.5)
Skin ulcer	53 (18.4)	50 (17.4)	36 (18.3)	43 (17.4)
Nasopharyngitis	36 (12.5)	49 (17.0)	28 (14.2)	33 (13.4)
Upper respiratory tract infection	33 (11.5)	35 (12.2)	27 (13.7)	26 (10.5)
Cough	34 (11.8)	52 (18.1)	24 (12.2)	21 (8.5)
Weight decreased	34 (11.8)	12 (4.2)	14 (7.1)	26 (10.5)
Abdominal pain	33 (11.5)	21 (7.3)	6 (3.0)	33 (13.4)
Liver test abnormalities	40 (13.9)	9 (3.1)	22 (11.2)	48 (19.4)

Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are shown based on single preferred terms except for 'liver test abnormalities', which was based on the standardised MedDRA query 'liver related investigations, signs and symptoms' (broad definition). Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 28 days after last drug intake if earlier in SENSCIS or until 7 days after last trial drug intake if earlier in SENSCIS-ON). Events reported in >10% of patients in either group in SENSCIS-ON are shown.

abnormalities were reported in 22 (11.2%) and 48 (19.4%) patients who continued and initiated nintedanib, respectively. Bleeding and cardiovascular adverse events are summarised in online supplemental table S2.

Serious adverse events were reported in 42 (21.3%) and 60 (24.3%) patients in the continued nintedanib and initiated nintedanib groups, respectively. The most frequent serious adverse event was pneumonia, reported in 8 (4.1%) and 4 (1.6%) patients who continued and initiated nintedanib, respectively (online supplemental table S3). The adverse event profile of nintedanib was generally similar in subgroups by mycophenolate use at the start of SENSCIS-ON (online supplemental table S4). Among patients who continued nintedanib, upper respiratory tract infections were more frequent (17.1% vs 9.8%) and vomiting less frequent (10.5% vs 17.4%) in the subgroup taking mycophenolate. Among patients who initiated nintedanib, nasopharyngitis was less frequent in patients taking mycophenolate (10.2% vs 16.7%). Cough was more frequent in the subgroup taking mycophenolate both among those who continued (15.2% vs 8.7%) and initiated (11.8% vs 5.0%) nintedanib. Liver test abnormalities were less frequent in patients taking mycophenolate both among those who continued (3.8% vs 19.6%) and initiated (13.4% vs 25.8%) nintedanib.

Among patients who continued and initiated nintedanib in SENSCIS-ON, respectively, 36 (18.3%) and 122 (49.4%) had ≥1 dose reduction and 55 (27.9%) and 104 (42.1%) had ≥1 treatment interruption. Among those who had ≥1 dose reduction, nine patients (25.0%) in the continued nintedanib group and eight patients (6.6%) in the initiated nintedanib group had ≥1 dose increase to 150 mg two times per day. Adverse events led to permanent discontinuation of nintedanib in nine patients (4.6%) who continued nintedanib and 53 patients (21.5%) who initiated nintedanib.

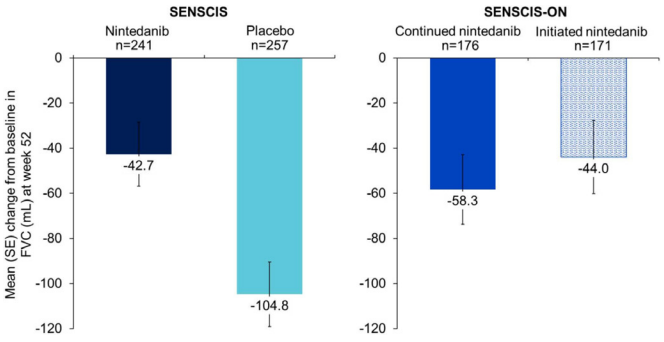
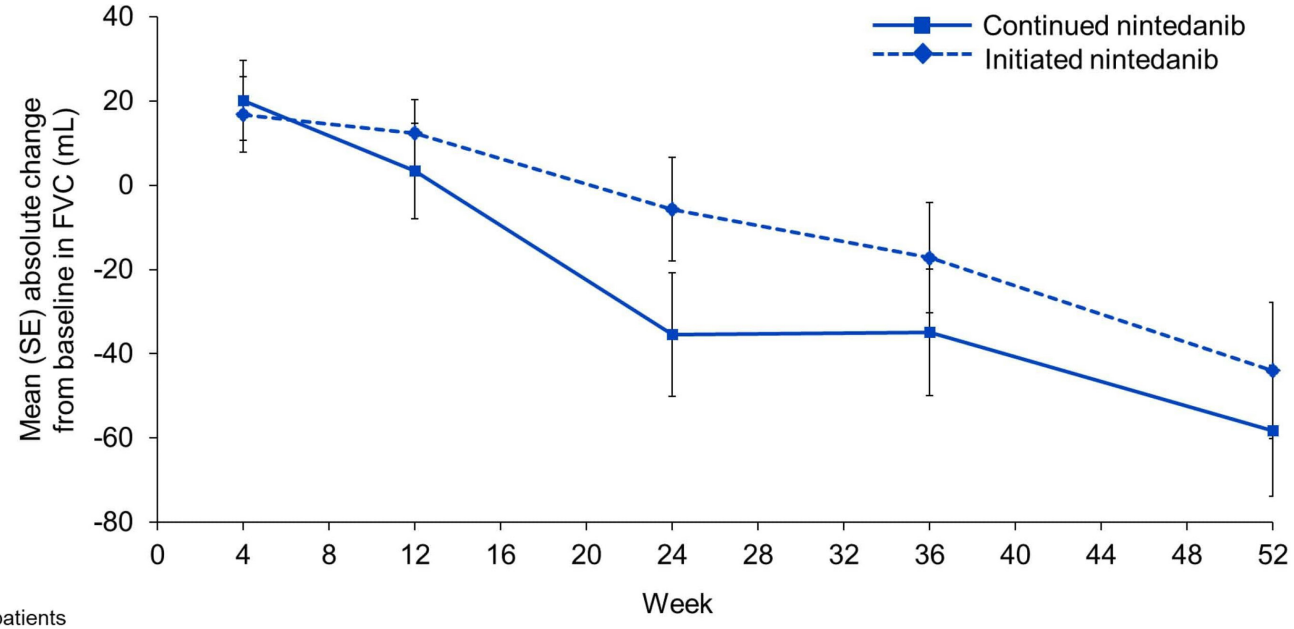


Figure 2 Change from baseline in FVC (mL) at week 52 in SENSCIS and SENSCIS-ON. Changes were based on data from patients with available data at baseline and at week 52. FVC, forced vital capacity.

Forced vital capacity

In total, 176 (89.3%) and 171 (69.2%) patients in the continued nintedanib and initiated nintedanib groups, respectively, had FVC data available at baseline and week 52. Mean (SE) changes in FVC from baseline to week 52 of SENSCIS-ON were −58.3 (15.5) mL in patients who continued nintedanib, −44.0 (16.2) mL in patients who initiated nintedanib and −51.3 (11.2) mL in all patients (figure 2). Changes in FVC over time in patients who continued and initiated nintedanib in SENSCIS-ON are shown in figure 3. Changes in FVC over time in SENSCIS and SENSCIS-ON are shown together in online supplemental figure S1. Changes in FVC over time based on pooled data from SENSCIS and SENSCIS-ON are shown in figure 4.

As patients remained in the SENSCIS trial until the last patient had reached week 52, the last few patients enrolled were treated for only 52 weeks in SENSCIS before transitioning into SENSCIS-ON. Thus, in the pooled analysis of changes in FVC over time, data after week 52 included data from patients treated with nintedanib or placebo in SENSCIS and patients treated with nintedanib in SENSCIS-ON. Of the patients who had FVC data available at baseline and at week 52, 13.6% of patients who continued nintedanib and 17.0% of patients who initiated nintedanib had an improvement in FVC (mL) ≥5% between baseline and week 52 of SENSCIS-ON (figure 5). A relative decline in FVC (mL) of >5% from baseline to week 52 of SENSCIS-ON was observed in 38.6% of patients who continued nintedanib and 29.2% of patients who initiated nintedanib; a relative decline in FVC (mL) of >10% occurred in 17.6% of patients who continued nintedanib and 12.9% of patients who initiated nintedanib. The cumulative distribution of patients by absolute change in FVC % predicted from baseline to week 52 of SENSCIS-ON is shown in online supplemental figure S2. Mean (SE) changes in



No. of patients						
Continued nintedanib	191	189	187	185	181	176
Initiated nintedanib	243	238	230	214	194	171

Figure 3 Absolute change from baseline in FVC (mL) over time in SENSCIS-ON. Baseline was the last measurement on or before the date of first trial drug intake in SENSCIS-ON. FVC, forced vital capacity.

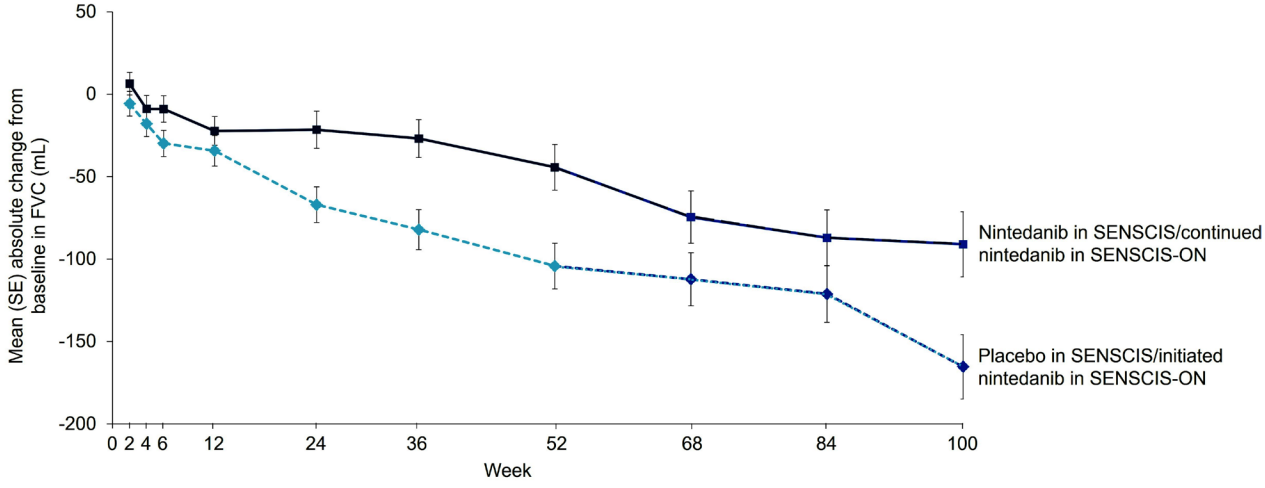
FVC in subgroups by mycophenolate use at the start of SENSCIS-ON are shown in online supplemental figure S3.

mRSS, SGRQ and UCLA SCTC GIT instrument

Mean (SE) change from baseline in mRSS at week 52 was −0.9 (0.2) in the continued nintedanib group (n=180) and −1.0 (0.3) in the initiated nintedanib group (n=174).

Mean (SE) change from baseline in SGRQ total score was 1.37 (0.87) in the continued nintedanib group (n=177) and −0.31 (0.91) in the initiated nintedanib group (n=183).

Mean (SE) change from baseline in UCLA SCTC GIT instrument total score was 0.28 (0.03) in the continued nintedanib group (n=168) and 0.18 (0.03) in the initiated nintedanib group (n=162).



No. of patients											
Nintedanib/continued nintedanib											
SENSCIS	288	283	280	271	271	255	246	232	154	110	64
Off treatment	0	0	1	2	7	10	16	24	17	12	11
SENSCIS-ON	0	0	0	0	0	0	0	0	61	101	119
Placebo/initiated nintedanib											
SENSCIS	288	283	281	279	281	274	260	256	169	107	69
Off treatment	0	0	0	1	2	6	8	11	10	10	6
SENSCIS-ON	0	0	0	0	0	0	0	0	72	120	130

Patients from the drug–drug interaction study were not included in this figure.
Patients remained in the SENSCIS trial until the last patient had reached week 52 but for ≤100 weeks. This meant that the last few patients enrolled in the SENSCIS trial were treated for only 52 weeks in SENSCIS before transitioning into SENSCIS-ON. In this pooled analysis, data from week 52 included data from patients treated with nintedanib or placebo in SENSCIS and patients treated with nintedanib in SENSCIS-ON. For patients who initiated nintedanib in SENSCIS-ON, the duration of placebo treatment in SENSCIS was 52 to 100 weeks and the duration of nintedanib treatment in SENSCIS-ON was 0 to 48 weeks.

Figure 4 Absolute change from baseline in FVC (mL) in SENSCIS and SENSCIS-ON (pooled). A digital version of this figure with a voiceover explaining the data is available at: https://www.globalmedcomms.com/respiratory/SENSCISandSENSCIS-ON. FVC, forced vital capacity.

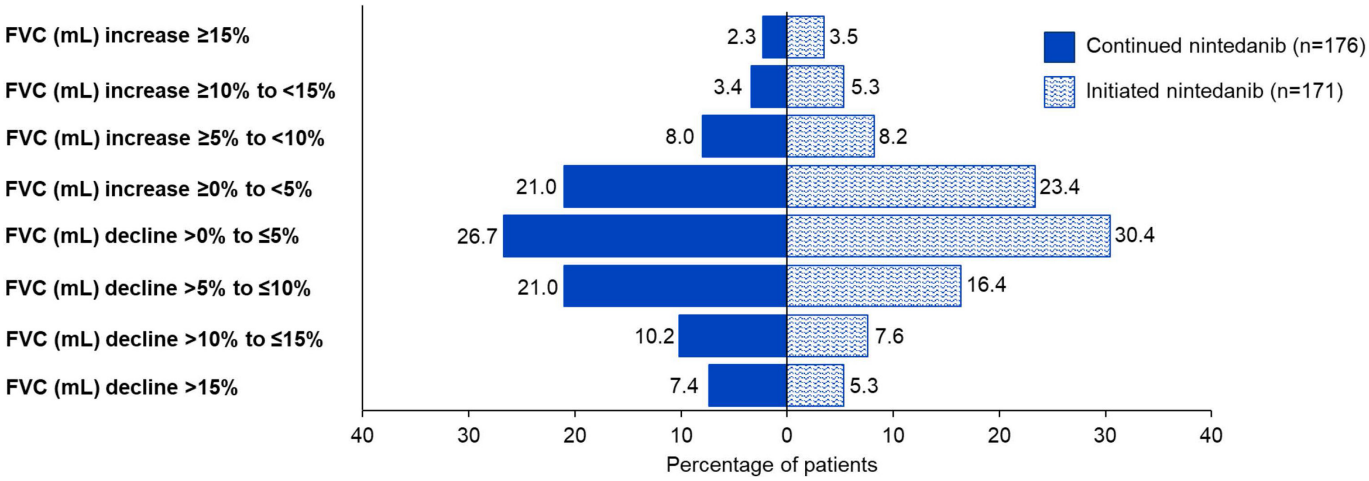


Figure 5 Proportions of patients with relative increases and declines in FVC (mL) from baseline to week 52 of SENSCIS-ON. Percentages were calculated using the number of patients with available data at baseline and at week 52 as the denominator. FVC, forced vital capacity.

DISCUSSION

Data from 52 weeks' follow-up in SENSCIS-ON showed that the adverse event profile of nintedanib over longer term use was consistent with that reported over 52 weeks in SENSCIS.[10 14] Among patients who initiated nintedanib in SENSCIS-ON, the proportions of patients who had a dose reduction or treatment interruption to manage adverse events over 52 weeks were similar to those observed in the nintedanib group of SENSCIS.[14] These dose adjustments were less frequent among the patients who continued nintedanib in SENSCIS-ON. Permanent discontinuations of nintedanib due to adverse events were also less frequent among patients who continued nintedanib in SENSCIS-ON than among those who initiated nintedanib in SENSCIS-ON or took nintedanib in SENSCIS. It is unclear whether the lower frequency of dose adjustments and discontinuations in the patients who continued nintedanib in SENSCIS-ON simply reflects that patients who were better able to tolerate the drug were more likely to have entered and continued in the trial, or whether there is improved tolerance to nintedanib with longer-term use.

Diarrhoea has consistently been shown to be the most frequent side effect of nintedanib in patients with ILDs.[10 18] Mild or moderate diarrhoea was the most frequently reported adverse event in SENSCIS-ON. Among patients who initiated nintedanib in SENSCIS-ON, 6.9% discontinued nintedanib due to diarrhoea over 52 weeks, consistent with the rate observed in patients who initiated nintedanib in SENSCIS. Discontinuation of nintedanib due to diarrhoea was less frequent among patients who continued nintedanib in SENSCIS-ON (1.5% over 52 weeks). Mean scores on the UCLA SCTC GIT instrument in both the continued nintedanib and initiated nintedanib groups suggested that most patients had no or mild gastrointestinal symptoms at the start of SENSCIS-ON.[17] A small worsening in mean UCLA SCTC GIT instrument total score was observed over 52 weeks. The adverse event profile of nintedanib was generally similar in patients who used nintedanib alone and in combination with mycophenolate, although the proportion of patients who had cough was higher in patients taking than not taking mycophenolate. This is consistent with the product label for mycophenolate, which reports cough as a side effect.

The change in FVC over 52 weeks of SENSCIS-ON was similar to the change in FVC over 52 weeks in the nintedanib group of SENSCIS (−51.3 and −42.7 mL, respectively) and much smaller than the change in FVC over 52 weeks in the placebo group of SENSCIS (−104.8 mL). Similar proportions of nintedanib-treated patients in SENSCIS and SENSCIS-ON had a decline in FVC from baseline of >5% and >10% over 52 weeks. These data, which suggest a sustained benefit of nintedanib on slowing the progression of SSc-ILD, are supported by data from the open-label extension of the INPULSIS trials, which suggested that the effect of nintedanib on slowing the progression of IPF persisted beyond 4 years.[19] The reduction in the rate of FVC decline provided by nintedanib in patients with SSc-ILD may be regarded as clinically meaningful given the disease trajectory and the known association between FVC decline and mortality in patients with SSc-ILD[3 5 6] and other ILDs.[20–22] Although the SENSCIS and SENSCIS-ON trials were not designed to investigate the effects of combination therapy, we note that the smallest decline in FVC over 52 weeks of SENSCIS-ON occurred in patients receiving both nintedanib and mycophenolate, consistent with observations in the SENSCIS trial.[23] Changes in the SGRQ total score in SENSCIS-ON were small, consistent with observations from SENSCIS[10] and from the INPULSIS trials in patients with IPF,[24] suggesting that the changes in FVC in SENSCIS-ON were not associated with a significant deterioration in respiratory symptoms.

Strengths of our analyses include the large cohort of patients who participated in SENSCIS-ON and the standardised collection of FVC measurements. About half of the patients who entered SENSCIS-ON were taking mycophenolate, increasing the relevance of our findings to clinical practice. Limitations of our analyses include the lack of a placebo group and the gradual loss of patients over the course of the trial. There may be selection bias among the patients who opted to participate in SENSCIS-ON, that is, these patients may have had fewer adverse events or better lung function; however, over 90% of patients who completed SENSCIS on treatment opted to participate in SENSCIS-ON. Although patients who participated in SENSCIS-ON were grouped according to their prior treatment, these are not randomised groups in SENSCIS-ON, so direct comparisons between patients who continued and initiated nintedanib should be approached with caution.

In conclusion, these data suggest that continued treatment with nintedanib, up to 3 years in duration, had a manageable safety and tolerability profile in patients with SSc-ILD. The adverse event profile of nintedanib over 52 weeks in SENSCIS-ON was consistent with that reported over the 52 weeks

of initial use in SENSCIS. The change in FVC in patients who received nintedanib over 52 weeks of SENSCIS-ON was similar to the change in FVC in patients who received nintedanib over 52 weeks in SENSCIS. These findings are consistent with a sustained clinically meaningful benefit of nintedanib in slowing the progression of SSc-ILD and support the prompt initiation of nintedanib in patients with SSc and pulmonary fibrosis.

Author affiliations
[1]Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France
[2]Department of Rheumatology, Radboud University Medical Center, Nijmegen, The Netherlands
[3]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[4]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
[5]Division of Rheumatology and Clinical Immunogenetics, University of Texas McGovern Medical School, Houston, Texas, USA
[6]Inflammation Medicine, Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland
[7]Elderbrook Solutions GmbH, Bietigheim-Bissingen, Germany
[8]Inflammation Medicine, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut, USA
[9]Inflammation Medicine, Boehringer Ingelheim International GmbH, Ingelheim, Germany
[10]Department of Medicine, University of Michigan Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA
[11]Pulmonary Medicine, Cleveland Clinic, Cleveland, Ohio, USA

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Patient and public involvement Patients were involved in the design and conduct of the SENSCIS trial and of its open-label extension, SENSCIS-ON (for example, by advising on the mouthpieces and blood draw needles that should be used). Patients' advice was also sought on the reporting of the results.

Patient consent for publication Not applicable.

Ethics approval The protocol was approved by an Ethics Committee or Institutional Review Board at all the participating centres (listed in the supplemental material). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs
Yannick Allanore http://orcid.org/0000-0002-6149-0002
Madelon C Vonk http://orcid.org/0000-0002-2266-9907
Oliver Distler http://orcid.org/0000-0002-0546-8310
Dinesh Khanna http://orcid.org/0000-0003-1412-4453

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Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON

Yannick Allanore, Madelon C Vonk, Oliver Distler, Arata Azuma, Maureen D Mayes, Martina Gahlemann, Alexandra James, Veronika Kohlbrenner, Margarida Alves, Dinesh Khanna, Kristin B Highland on behalf of the SENSCIS-ON trial investigators

Supplemental material

Contents

A. Exclusion criteria for SENSCIS-ON

Patients who met any of the following criteria were not eligible:

1. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN)
2. Bilirubin >2 times the ULN
3. Creatinine clearance <30 mL/min calculated per Cockcroft-Gault formula
4. Clinically relevant anaemia
5. Bleeding risk, i.e. any of the following:
    a. Known genetic predisposition to bleeding
    b. Patients who required:
        i. Fibrinolysis, full-dose therapeutic anticoagulation
        ii. High-dose antiplatelet therapy
    c. Haemorrhagic central nervous system event after completion of the parent trial
    d. Any of the following after last treatment in the parent trial:
        i. Haemoptysis or haematuria
        ii. Active gastrointestinal bleeding or gastrointestinal ulcers
        iii. Gastric antral vale ectasia
        iv. Major injury or surgery
    e. Coagulation parameters: international normalised ratio >2, prolongation of prothrombin time and partial thromboplastin time by >1.5 time the ULN
6. New major thrombo-embolic events developed after completion of the parent trial:
    a. Stroke
    b. Deep vein thrombosis
    c. Pulmonary embolism
    d. Myocardial infarction

7. Major surgery (according to the investigator's assessment) to be performed within the next 3 months
8. >12 weeks between last drug intake in SENSCIS, or >1 week between last nintedanib intake in the drug–drug interaction study, and initiation of nintedanib in SENSCIS-ON
9. Usage of any investigational drug after completion of the parent trial, or planned usage of an investigational drug during SENSCIS-ON
10. A disease or condition which in the opinion of the investigator may put the patient at risk or limit the patient's ability to participate in this trial
11. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial patient or unlikely to complete the trial
12. Known hypersensitivity to nintedanib
13. Women who were pregnant, nursing, or who planned to become pregnant while in the trial
14. Previous enrolment in SENSCIS-ON

B. Table S1. Baseline characteristics of patients in SENSCIS-ON in subgroups by mycophenolate use

	Taking mycophenolate		Not taking mycophenolate	
	Continued nintedanib (n=105)	Initiated nintedanib (n=127)	Continued nintedanib (n=92)	Initiated nintedanib (n=120)
Female, n (%)	74 (70.5)	94 (74.0)	74 (80.4)	93 (77.5)
Age, years, mean (SD)	53.9 (10.8)	52.3 (11.9)	58.0 (11.4)	56.7 (12.4)
Weight, kg, mean (SD)	72.5 (14.8)	72.2 (17.4)	63.0 (14.2)	69.1 (15.5)
Body mass index, kg/m^2, mean (SD)	26.7 (4.6)	26.3 (5.5)	24.0 (4.3)	25.9 (4.9)
Race, n (%)				
White	87 (82.9)	99 (78.0)	55 (59.8)	67 (55.8)
Asian	7 (6.7)	17 (13.4)	35 (38.0)	51 (42.5)
Black or African-American	7 (6.7)	8 (6.3)	2 (2.2)	1 (0.8)
Other	4 (3.8)	3 (2.4)	0	1 (0.8)
FVC, mL, mean (SD)	2379 (704)	2460 (863)	2379 (812)	2426 (763)
FVC, % predicted, mean (SD)	67.7 (16.8)	68.6 (18.7)	73.5 (19.1)	73.0 (16.8)
mRSS, mean (SD)	9.6 (8.0)	8.9 (8.0)	7.3 (7.1)	8.6 (7.7)
SGRQ total score, mean (SD)	46.0 (21.0)	40.5 (22.4)	36.4 (19.0)	34.8 (21.0)
UCLA SCTC GIT instrument total score, mean (SD)	0.33 (0.33)	0.38 (0.34)	0.32 (0.34)	0.28 (0.33)

C. Table S2. Bleeding and cardiovascular adverse events in SENSCIS and SENSCIS-ON

	SENSCIS		SENSCIS-ON	
	Nintedanib (n=288)	Placebo (n=288)	Continued nintedanib (n=197)	Initiated nintedanib (n=247)
Bleeding*	32 (11.1)	24 (8.3)	20 (10.2)	20 (8.1)
Hypertension†	14 (4.9)	5 (1.7)	11 (5.6)	5 (2.0)
Major adverse cardiovascular events‡	4 (1.4)	5 (1.7)	5 (2.5)	5 (2.0)
Venous thromboembolism†	4 (1.4)	3 (1.0)	0	1 (0.4)
Haemorrhagic and ischaemic stroke†	3 (1.0)	1 (0.3)	1 (0.5)	1 (0.4)
Arterial thromboembolism†	2 (0.7)	2 (0.7)	0	1 (0.4)
QT prolongation†	2 (0.7)	0	1 (0.5)	0
Myocardial infarction†	0	2 (0.7)	0	1 (0.4)
Cardiac failure†	1 (0.3)	1 (0.3)	4 (2.0)	2 (0.8)

Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 28 days after last drug intake if earlier in SENSCIS or until 7 days after last trial drug intake if earlier in SENSCIS-ON). *Based on pooled MedDRA terms. †Narrow standardised MedDRA query. ‡Based on fatal adverse events in the MedDRA system organ classes “cardiac disorders” and “vascular disorders”; any fatal and non-fatal events in the subordinate standardised MedDRA query “myocardial infarction” (broad); any fatal and non-fatal stroke events (based on selected MedDRA preferred terms); and the MedDRA preferred terms “sudden death”, “cardiac death” and “sudden cardiac death”.

D. Table S3. Serious adverse events (reported irrespective of causality) in SENSCIS and SENSCIS-ON

	SENSCIS		SENSCIS-ON	
	Nintedanib (n=288)	Placebo (n=288)	Continued nintedanib (n=197)	Initiated nintedanib (n=247)
Pneumonia	8 (2.8)	1 (0.3)	8 (4.1)	4 (1.6)
Dyspnoea	3 (1.0)	5 (1.7)	2 (1.0)	3 (1.2)
Pulmonary hypertension	4 (1.4)	4 (1.4)	4 (2.0)	1 (0.4)
Liver injury	0	0	0	4 (1.6)
Diarrhoea	2 (0.7)	2 (0.7)	0	3 (1.2)
Skin ulcer	1 (0.3)	2 (0.7)	3 (1.5)	0
Pulmonary arterial hypertension	3 (1.0)	0	1 (0.5)	2 (0.8)
Drug-induced liver injury	1 (0.3)	1 (0.3)	0	3 (1.2)
Hepatic enzyme increased	0	0	0	3 (1.2)
Atrial fibrillation	1 (0.3)	1 (0.3)	1 (0.5)	2 (0.8)
Pulmonary fibrosis	3 (1.0)	4 (1.4)	0	2 (0.8)
Vomiting	0	2 (0.7)	0	2 (0.8)
Pneumothorax	1 (0.3)	0	0	2 (0.8)
Chest pain	0	0	0	2 (0.8)
Cholelithiasis	0	0	0	2 (0.8)
Basal cell carcinoma	1 (0.3)	0	0	2 (0.8)
Breast cancer	0	0	2 (1.0)	0
Lung neoplasm malignant	0	0	2 (1.0)	0

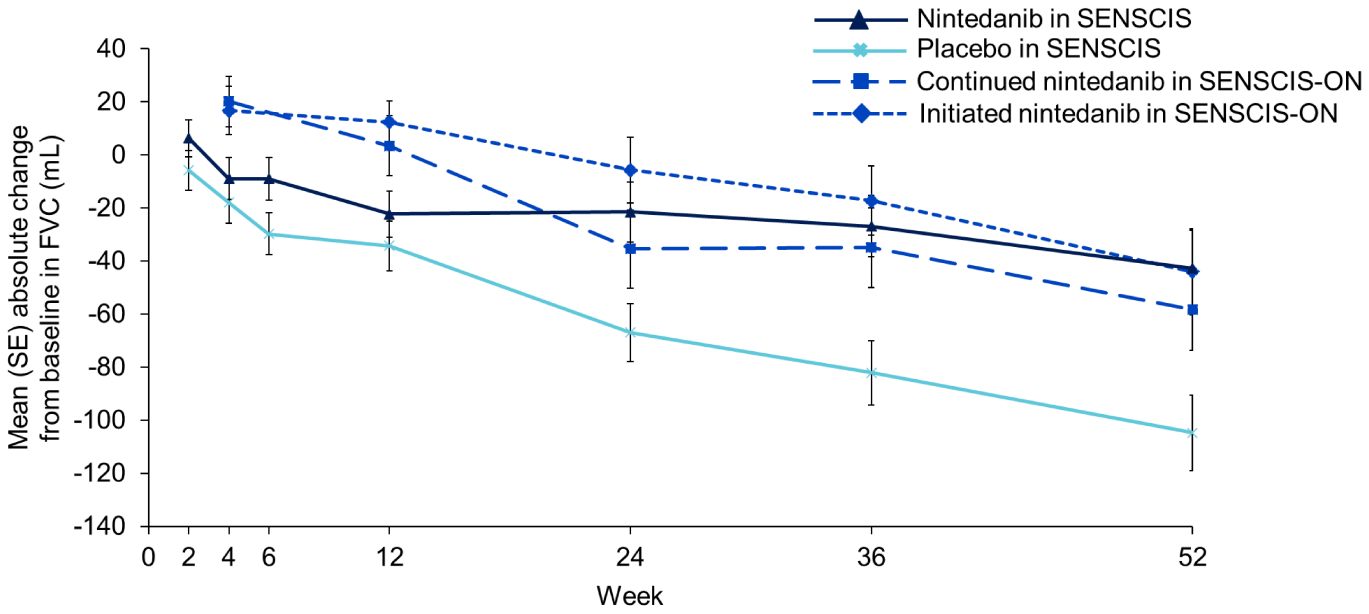
Serious adverse events were defined as adverse events that resulted in death, were life threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed to be serious for any other reason. Serious adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are shown based on single preferred terms. Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 28 days after last drug intake if earlier in SENSCIS or until 7 days after last trial drug intake if earlier in SENSCIS-ON). Events reported in ≥2 patients in either group in SENSCIS-ON are shown.

E. Table S4. Adverse events (reported irrespective of causality) in SENSCIS-ON by mycophenolate use at baseline

	Taking mycophenolate		Not taking mycophenolate	
	Continued nintedanib (n=105)	Initiated nintedanib (n=127)	Continued nintedanib (n=92)	Initiated nintedanib (n=120)
Diarrhoea	71 (67.6)	89 (70.1)	63 (68.5)	81 (67.5)
Nausea	15 (14.3)	29 (22.8)	17 (18.5)	31 (25.8)
Vomiting	11 (10.5)	30 (23.6)	16 (17.4)	23 (19.2)
Skin ulcer	20 (19.0)	22 (17.3)	16 (17.4)	21 (17.5)
Nasopharyngitis	13 (12.4)	13 (10.2)	15 (16.3)	20 (16.7)
Upper respiratory tract infection	18 (17.1)	16 (12.6)	9 (9.8)	10 (8.3)
Cough	16 (15.2)	15 (11.8)	8 (8.7)	6 (5.0)
Weight decreased	8 (7.6)	16 (12.6)	6 (6.5)	10 (8.3)
Abdominal pain	3 (2.9)	19 (15.0)	3 (3.3)	14 (11.7)
Liver test abnormalities	4 (3.8)	17 (13.4)	18 (19.6)	31 (25.8)

Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events are shown based on single preferred terms except for “liver test abnormalities”, which was based on the standardised MedDRA query “liver related investigations, signs and symptoms” (broad definition). Data are n (%) of patients with ≥1 such event reported over 52 weeks (or until 7 days after last trial drug intake if earlier). Events reported in >10% of patients in the continued nintedanib or initiated nintedanib groups in the overall population are shown.

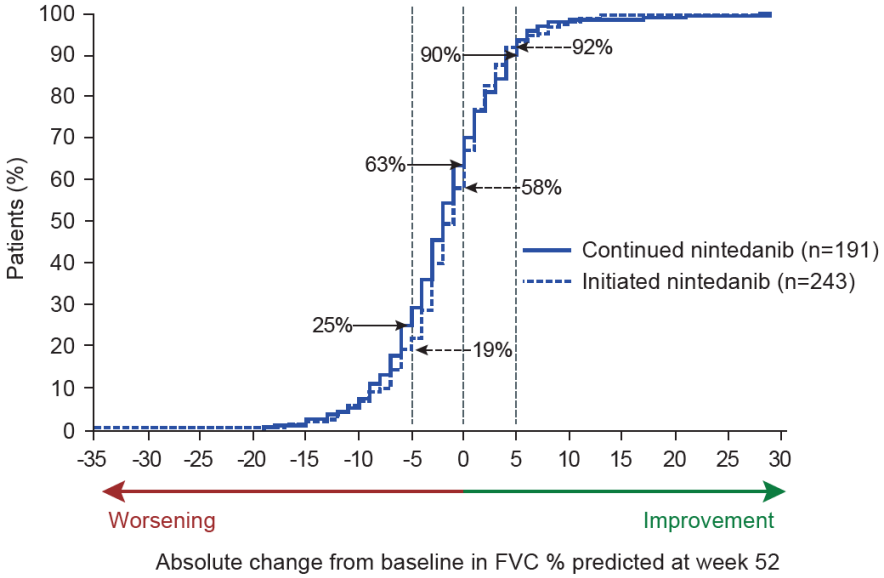
F. Figure S1. Change from baseline in FVC (mL) over time in SENSCIS and SENSCIS-ON



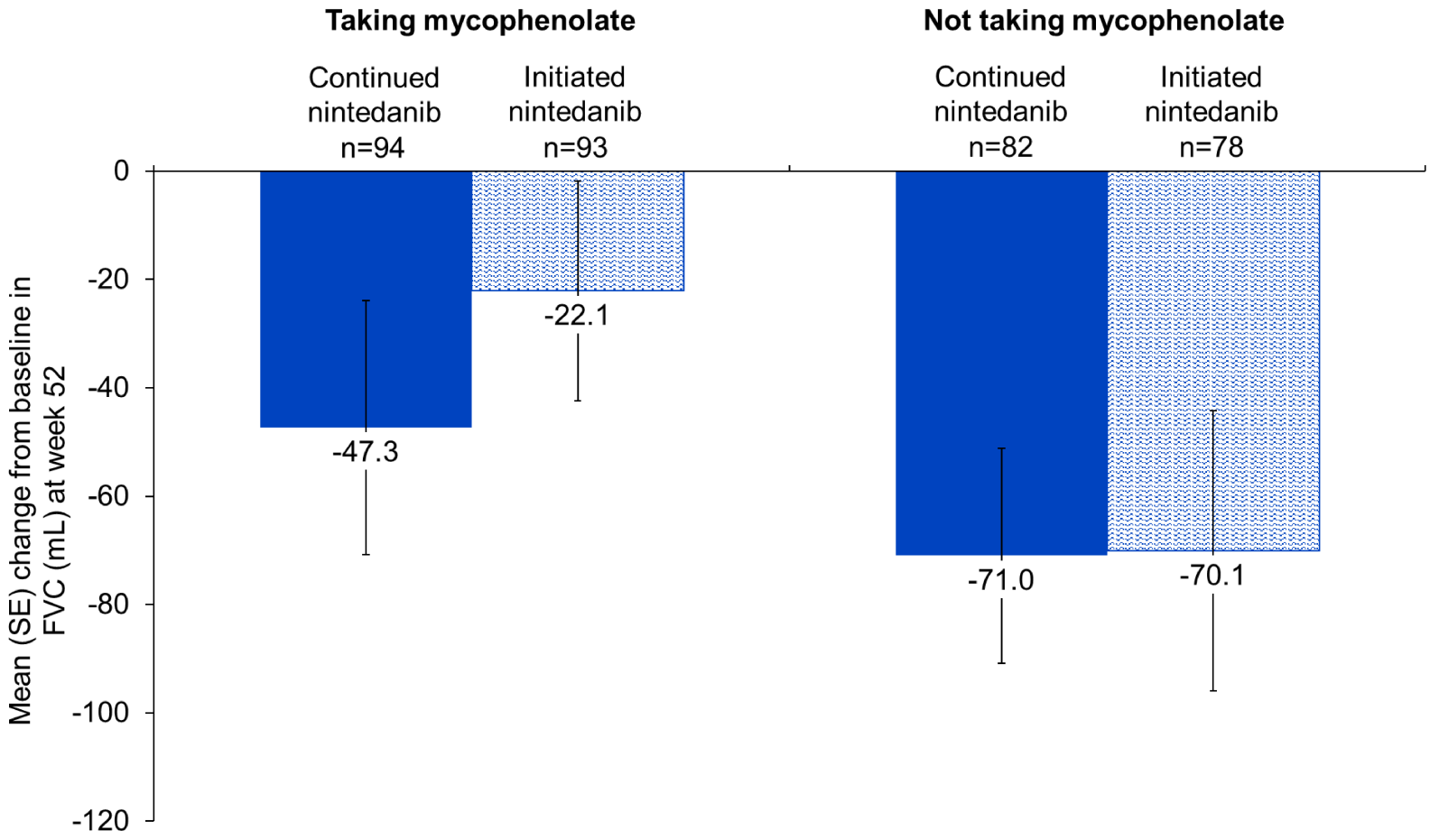
No. of patients								
SENSCIS								
Nintedanib	288	283	281	273	278	265	262	241
Placebo	288	283	281	280	283	280	268	257
SENSCIS-ON								
Continued nintedanib	191		189		187	185	181	176
Initiated nintedanib	243		238		230	214	194	171

Patients who completed the SENSCIS trial on treatment and attended a follow-up visit 28 days later were eligible to participate in SENSCIS-ON.
Baseline in SENSCIS-ON was the last measurement on or before the date of first trial drug intake in SENSCIS-ON.

G. Figure S2. Cumulative distribution of patients by change in FVC from baseline to week 52 of SENSCIS-ON



H. Figure S3. Change from baseline in FVC (mL) at week 52 in SENSCIS-ON by mycophenolate use at baseline



Changes were based on data from patients with available data at baseline and at week 52.

I. Data availability

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent.

Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing

J. SENSCIS-ON trial sites

Argentina: APRILLUS, Buenos Aires; CEMER-Centro Medico De Enfermedades Respiratorias, Buenos Aires; Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich, Buenos Aires. **Australia:** St Vincent's Hospital Melbourne, Fitzroy; Royal Adelaide Hospital, Adelaide; Liverpool Hospital, Liverpool; Royal Prince Alfred Hospital, Camperdown. **Austria:** Medical University of Innsbruck, Innsbruck. **Belgium:** UZ Leuven, Leuven; Centre Hospitalier Universitaire de Liège, Liège. **Brazil:** Edumed - Educacao e Saude SA, Curitiba. **Canada:** Hôpital du Sacré-Coeur, Quebec. **Chile:** Centro de Investigación del Maule, Talca; Hospital Clínico Regional de Concepción "Dr. Guillermo Grant Benavente", Concepción. **China:** Peking Union Medical College Hospital, Beijing; The First Hospital of China Medical University, Shenyang City; The First Hospital of Jilin University, Changchun City; West China Hospital, Chengdu City; Huashan Hospital, Fudan University, Shanghai; The First Affiliated Hospital of Anhui Medical University, Hefei City. **Czech Republic:** Institute of Rheumathology Prague, Prague. **Denmark:** Aarhus University Hospital, Aarhus; Odense University Hospital, Odense. **Finland:** HYKS, Keuhkosairauksien yksikkö, Helsinki; TYKS, Keuhkosairauksien klinikka, T-sairaala, Turku. **France:** CHU Rouen - Hôpital Charles Nicolle, Rouen; Hôpital Arnaud de Villeneuve, Montpellier; Hôpital Larrey, Toulouse; Hôpital Albert Calmette, Lille; Hôpital Hôtel-Dieu - CHU de Nantes, Nantes; CHRU LILLE - Hôpital Claude Huriez, Lille; Hôpital Pasteur, Nice; Hôpital Pontchaillou, Rennes; Hôpital Bichat, Paris; CHRU de Bretonneau, Tours; Groupement Hospitalier Est - Hôpital Louis Pradel, Bron; Hôpital Cochin, Paris; Hôpital Avicenne, Bobigny. **Germany:** Universitätsklinikum Schleswig-Holstein Campus Kiel, Kiel; Universitätsklinikum Münster, Münster; Universitätsklinikum Carl Gustav Carus der Technischen Universität Dresden, Dresden; Klinik Donaustauf, Donaustauf; Universitätsmedizin Greifswald, Greifswald; Universitätsklinikum Erlangen, Erlangen; Asklepios Kliniken Hamburg GmbH, Hamburg; Medizinische Hochschule Hannover, Hannover; Universitätsklinikum Tübingen, Tübingen; Thoraxklinik-Heidelberg GmbH am Universitätsklinikum, Heidelberg. **Greece:** General Hospital of Athens "Laiko", Athens. **India:** Getwell Hospital & Research Institute, Nagpur; Care Hospital, Banjara Hills, Hyderabad; Postgraduate Institute of Medical Education and Research, Chandigarh; SIR Gangaram Hospital, New Delhi; All India Institute of Medical Science, New Delhi; B.J. Medical College and Sasoon General Hospital, Pune; Asthma Bhawan, Jaipur; Ramaiah Medical College and Hospitals, Bangalore; Nizam's Institute of Medical Sciences, Hyderabad. **Israel:** Sourasky Tel Aviv Medical Center Rheumatology Department, Tel Aviv; Rabin Medical Center Beilinson, Petah Tiqwa; Bnai Zion Medical Center, Haifa; Rambam Medical Center Rheumatology Department, Haifa. **Italy:** A.O. San Gerardo di Monza, Monza; Azienda Universitaria-Universita' La Sapienza, Roma; Università degli Studi di Padova, Padova; Università degli Studi di Genova, Genova; A.O Universitaria – Università degli Studi della Campania Luigi Vanvitelli, Campania. **Japan:** Sapporo Medical University Hospital, Hokkaido; Toho University Omori Medical Centre, Tokyo; Nippon Medical School Hospital, Tokyo; St. Marianna University School of Medicine Hospital, Kanagawa; Kitasato University Hospital, Kanagawa; Kanagawa Cardiovascular and Respiratory Center, Kanagawa; Hamamatsu University Hospital, Shizuoka; Tosei General Hospital, Aichi; Osaka Medical College Hospital, Osaka; National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka; Kindai University Hospital, Osaka; National Hospital Organization Himeji Medical Center, Hyogo; Tokushima University Hospital, Tokushima; Kurume University Hospital, Fukuoka; Nagasaki University Hospital, Nagasaki; Saitama Medical University Hospital, Saitama; Institute of Rheumatology Tokyo Women's

Medical University, Tokyo; Juntendo University Hospital, Tokyo. **Malaysia:** Hospital Pulau Pinang, Pulau Pinang; University Malaya Medical Centre, Kuala Lumpur. **México:** Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Ciudad de México. **Netherlands:** Leids Universitair Medisch Centrum (LUMC), Leiden; Radboud Universitair Medisch Centrum, Nijmegen; VU Medisch Centrum, Amsterdam; Erasmus Medisch Centrum, Rotterdam. **Norway:** Oslo Universitetssykehus HF, Rikshospitalet, Oslo; Nord-Norge, Tromsø. **Poland:** Independent Public Clinical Hospital No.1 in Wroclaw, Wroclaw; Dr Jan Biziel Universisty Hospital No. 2, Bydgoszcz; EMED, Center of Medical Services private practice, Rzeszow; Specialist Allergy-Internist Center ALL-MED, Krakow. **Portugal:** Centro Hospitalar e Universitário de Coimbra, Coimbra; Hospital Fernando Fonseca, Amadora; Centro Hospitalar de São João, Porto; Hospital Garcia de Orta, Almada; ULSAM, EPE-Hospital Conde de Bertiandos, Ponte de Lima; Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia. **Spain:** Hospital Universitario Dr Peset, Valencia; Hospital Universitario 12 de Octubre, Madrid; Hospital Santa Creu i Sant Pau, Barcelona; Hospital Universitari Vall d'Hebron, Barcelona; Hospital General Universitario Gregorio Marañón, Madrid; Hospital Universitario y Politécnico La Fe, Valencia; Hospital Álvaro Cunqueiro, Vigo. **Sweden:** Sahlgrenska University Hospital, Gothenburg. **Switzerland:** Universitätsspital Zürich, Zürich. **Thailand:** Songklanagarind Hospital, Hat Yai; Srinagarind Hospital, Muang; Ramathibodi Hospital, Ratchathewi. **United Kingdom:** Royal Free Hospital, London; Salford Royal Hospital, Salford; Royal Brompton Hospital, London; Guy's Hospital, London. **United States:** Cleveland Clinic, Cleveland; Vanderbilt University Medical Center, Nashville; Virginia Mason Medical Center, Seattle; Tulane University Hospital and Clinic, New Orleans; Georgetown University Clinical Research Unit, Washington; Mayo Clinic, Rochester; Duke University Medical Center, Durham; Froedtert and The Medical College of Wisconsin, Milwaukee; Boston University School of Medicine, Boston; Yale University School of Medicine, New Haven; University of Kansas Medical Center, Kansas City; Thomas Jefferson University, Philadelphia; University of California Davis, Sacramento; Columbia University Medical Center-New York Presbyterian Hospital, New York; University of Iowa Hospitals and Clinics, Iowa City; University of Pennsylvania, Philadelphia; The University of Texas at Houston, Houston; Stanford University Medical Center, Stanford; The Emory Clinic, Atlanta; University of California San Francisco, San Francisco; University of Miami Pulmonary Research Office, Miami; University of Alabama at Birmingham Lung Health Center, Birmingham; University of California Los Angeles, Los Angeles; Northwestern University, Chicago; University of Toledo, Toledo; Washington University School of Medicine, St. Louis; Hospital for Special Surgery Division of Rheumatology, New York; University of Cincinnati, Cincinnati; Johns Hopkins Hospital, Baltimore; University of Minnesota Masonic Cancer Center, Minneapolis; Temple University Hospital, Philadelphia; University of Utah Health Sciences Center, Salt Lake City; University of Washington Medical Center, Seattle; Medical University of South Carolina, Charleston; University of Florida College of Medicine, Jacksonville; University of Colorado Hospital, Aurora; Inova Fairfax Medical Campus, Falls Church; University of Texas Southwestern Medical Center, Dallas; Icahn School of Medicine at Mount Sinai, New York.

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Nintedanib long-term safety data in people with interstitial lung disease

The safety profile of nintedanib was consistent with that reported in a previous trial

INTRODUCTION

Systemic sclerosis is an autoimmune disease that causes abnormalities in the skin, joints, and internal organs, including the lungs. It is associated with changes in blood vessels that causes scarring or thickening in affected tissues, such as the skin and lungs. Systemic sclerosis is more common in women than men, and most often develops between the ages of 30–50 years.

Involvement of lung tissue often develops early in the disease. This so called systemic sclerosis-associated interstitial lung disease (shortened to SSc-ILD) has a variable course and can worsen over time in some people. SSc-ILD is characterised by an increase in scarring and a decline in a measure of lung function called *forced vital capacity* (shortened to FVC). This is the maximum amount of air you can push out from your lungs after taking a full breath.

Results from a previous trial showed that a drug called nintedanib reduced the rate of decline in people's FVC over 1 year. Nintedanib inhibits a protein within cells called tyrosine kinase, and therefore has anti-inflammatory properties, as well as being anti-scarring or anti-fibrotic.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to monitor people's FVC and the picture of adverse events (side effects) during a longer period of treatment than the 1 year of the original study.

WHO WAS STUDIED?

The study looked at 473 people with SSc-ILD. Everyone had already taken part in an earlier trial, where they had received either nintedanib or placebo for at least 1 year, and then transitioned into a second year of treatment.

HOW WAS THE STUDY CONDUCTED?

This was an open-label extension study. This means that both patients and their doctors knew which group they were in.

In the original trial, people had been divided ("randomised") to receive either nintedanib 150 mg twice per day or placebo for 1 year. In the extension, everyone received nintedanib for a further year. This means people were in one of two groups – the *continuers*, who received the drug for a full 2-year period, and the *initiators*, who received placebo in the original trial, and then were switched to nintedanib in the extension period.

The authors compared the long-term FVC results between these two groups. They also evaluated adverse events and side effects.

WHAT WAS THE MAIN FINDING?

The main finding was that the adverse events and side effects of nintedanib in the extension study were consistent with those reported in the original trial. Diarrhoea was reported in about 70% of both continuers and initiators. Overall, nintedanib had to be permanently stopped in 5% of continuers and 22% of initiators.

The change in FVC was also similar to that observed in the nintedanib group in the original trial. Mean changes were a decrease of 58 millilitres in the volume that could be forced out of the lungs for continuers, and a decrease of 44 millilitres for initiators. Both these declines were much less than what had been seen for people taking placebo in the original trial.

ARE THESE FINDINGS NEW?

Yes, these are new findings.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

One limitation is that efficacy cannot be accurately measured in this kind of open-label study due to a lack of a placebo group, so long-term efficacy will have to be further investigated. Further limitations of the analyses include the gradual loss of patients over the course of the trial and the selection bias potentially related to the fact that people who agreed to take part may have had fewer adverse events or better lung function in the first place.

WHAT DO THE AUTHORS PLAN TO DO WITH THIS INFORMATION?

The authors suggest that in clinical practice nintedanib should be started quickly in people with SSc-ILD to slow the usual decline in lung function that is seen in this disease.

WHAT DOES THIS MEAN FOR ME?

If you have SSc-ILD, there are new treatment options on the horizon. The right treatment decision for you will be made on a case-by-case basis, taking into account the severity of your lung disease, risk factors for progression, any other manifestations of your systemic sclerosis, and your personal preferences.

If you have any questions about your disease or its treatment, speak to your healthcare team.

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From: Allanone Y, *et al*. Continued treatment with nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from SENSCIS-ON. Ann Rheum Dis 2022;81(12):1722–9. doi:10.1136/annrheumdis-2022-222564