ORIGINAL ARTICLE

# Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

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## ABSTRACT

### BACKGROUND

Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis–related death. Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and antiinflammatory effects in preclinical models of systemic sclerosis and ILD.

### METHODS

We conducted a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of nintedanib in patients with ILD associated with systemic sclerosis. Patients who had systemic sclerosis with an onset of the first non-Raynaud's symptom within the past 7 years and a high-resolution computed tomographic scan that showed fibrosis affecting at least 10% of the lungs were randomly assigned, in a 1:1 ratio, to receive 150 mg of nintedanib, administered orally twice daily, or placebo. The primary end point was the annual rate of decline in forced vital capacity (FVC), assessed over a 52-week period. Key secondary end points were absolute changes from baseline in the modified Rodnan skin score and in the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52.

### RESULTS

A total of 576 patients received at least one dose of nintedanib or placebo; 51.9% had diffuse cutaneous systemic sclerosis, and 48.4% were receiving mycophenolate at baseline. In the primary end-point analysis, the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P=0.04). Sensitivity analyses based on multiple imputation for missing data yielded P values for the primary end point ranging from 0.06 to 0.10. The change from baseline in the modified Rodnan skin score and the total score on the SGRQ at week 52 did not differ significantly between the trial groups, with differences of −0.21 (95% CI, −0.94 to 0.53; P=0.58) and 1.69 (95% CI, −0.73 to 4.12 [not adjusted for multiple comparisons]), respectively. Diarrhea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group.

### CONCLUSIONS

Among patients with ILD associated with systemic sclerosis, the annual rate of decline in FVC was lower with nintedanib than with placebo; no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis. The adverse-event profile of nintedanib observed in this trial was similar to that observed in patients with idiopathic pulmonary fibrosis; gastrointestinal adverse events, including diarrhea, were more common with nintedanib than with placebo. (Funded by Boehringer Ingelheim; SENSCIS ClinicalTrials.gov number, NCT02597933.)

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This article was published on May 20, 2019, at NEJM.org.

N Engl J Med 2019;380:2518-28.
DOI: 10.1056/NEJMoa1903076

Systemic sclerosis is a rare and heterogeneous autoimmune disease characterized by immune dysregulation, microvascular damage, and organ fibrosis.[1] Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis that tends to occur early in the course of disease[2,3]; the condition places a considerable burden on patients and health care resources[4,5] and is a leading cause of death related to systemic sclerosis.[6] On the basis of evidence from two randomized, double-blind trials (Scleroderma Lung Studies I and II [SLS-I and SLS-II]),[7,8] the immunosuppressants mycophenolate and cyclophosphamide are frequently used for the treatment of ILD associated with systemic sclerosis. In addition, targeted treatments are licensed to address other organ manifestations such as pulmonary arterial hypertension and digital ulcers.

Nintedanib, an intracellular inhibitor of tyrosine kinases,[9] is an approved treatment for idiopathic pulmonary fibrosis. In patients with idiopathic pulmonary fibrosis, treatment with nintedanib (150 mg twice daily) slowed disease progression by reducing the rate of decline of the forced vital capacity (FVC).[10,11] Although idiopathic pulmonary fibrosis and ILD associated with systemic sclerosis have different triggers, the pathophysiological processes of both diseases include the transformation of fibroblasts to a myofibroblastic phenotype and the excess deposition of extracellular matrix.[12-15] Nintedanib has shown antifibrotic, antiinflammatory, and vascular remodeling effects in several animal models resembling aspects of systemic sclerosis, ILD associated with systemic sclerosis, and other fibrosing ILDs,[9,15-21] findings that suggest that nintedanib could modulate processes fundamental to the progression of fibrosis in humans. We conducted the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial to investigate the efficacy and safety of nintedanib in patients with ILD associated with systemic sclerosis.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The SENSCIS trial was a randomized, double-blind, placebo-controlled, parallel-group trial that was performed in 32 countries.[22] The trial was conducted in accordance with the trial protocol (available with the full text of this article at NEJM.org), 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 authors had access to the data, which were analyzed by the trial sponsor, Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version for submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The statistical analysis plan is available with the protocol at NEJM.org. Medical writing assistance, paid for by the sponsor, was provided by FleishmanHillard Fishburn.

### PATIENTS

Patients were recruited from November 2015 through October 2017 and were eligible for enrollment if they were at least 18 years of age and had systemic sclerosis according to classification criteria of the American College of Rheumatology and European League Against Rheumatism,[1] with an onset of the first non-Raynaud's symptom within 7 years before screening. ILD was identified on the basis of a high-resolution computed tomographic scan, obtained within 12 months before screening, that showed fibrosis affecting at least 10% of the lungs, as confirmed by an expert radiologist at a central location. Patients were required to have an FVC that was at least 40% of the predicted value and a diffusion capacity of the lung for carbon monoxide ($DL_{CO}$) (corrected for hemoglobin) that was 30 to 89% of the predicted value. Patients who were receiving prednisone at a dose of up to 10 mg per day or mycophenolate or methotrexate at a stable dose for at least 6 months before randomization (or both therapies) could participate in the trial. If clinically significant worsening of systemic sclerosis occurred during the trial, additional therapy was allowed (see section B in the Supplementary Appendix, available at NEJM.org). Key exclusion criteria are listed in section C in the Supplementary Appendix. Of the 819 patients screened, 4 who had clinically significant pulmonary hypertension (defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization with a cardiac index of ≤2 liters per

minute per square meter of body-surface area, or pulmonary hypertension that led to parenteral therapy with epoprostenol or treprostinil) were excluded.

### RANDOMIZATION AND PROCEDURES

After a screening period of 12 weeks or less, patients were randomly assigned, in a 1:1 ratio, to receive 150 mg of nintedanib, administered orally twice daily, or placebo. Randomization was performed with the use of an interactive response system, and the patients were stratified according to the presence of antitopoisomerase I antibody, which has been associated with a decline in FVC in patients with early systemic sclerosis.[23] The primary efficacy evaluation was conducted at week 52. Patients continued to receive the assigned intervention in a blinded manner until the last patient reached week 52 but for no longer than 100 weeks. Patients who discontinued the intervention were asked to attend all scheduled visits and undergo examinations as originally planned. Patients who had adverse events were permitted to interrupt the course of their assigned intervention (for ≤4 weeks if they had an adverse event that was considered to be related to the intervention by the investigator or for ≤8 weeks for adverse events that were not considered to be related to the intervention) or to reduce the dose to 100 mg twice daily.

### END POINTS

The primary end point was the annual rate of decline in FVC (milliliters per year), assessed over a 52-week period and analyzed with a random-coefficient regression model. Key secondary end points were absolute changes from baseline in the modified Rodnan skin score and the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 52. The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis.[24,25] The minimal clinically important difference in modified Rodnan skin score in patients with ILD associated with systemic sclerosis has not been established but has been suggested to be 3 to 4 points.[26] The SGRQ is a 50-item questionnaire that is administered by the patients themselves. The questionnaire comprises three domains (symptoms, activity, and impact) that assess health-related quality of life in patients with respiratory disease.[27] Domain and total scores range from 0 to 100, with higher scores indicating worse health-related quality of life. The minimal clinically important difference in SGRQ total score in patients with ILD associated with systemic sclerosis has not been established, but a change of 4 points or more may represent a meaningful change in patients with idiopathic pulmonary fibrosis.[28]

Other prespecified secondary end points included the annual rate of decline in FVC as a percentage of the predicted value; the absolute change from baseline in FVC (measured in milliliters) at week 52; the absolute change from baseline in $DL_{CO}$ as a percentage of the predicted value at week 52; the absolute changes from baseline in net digital ulcer burden (the number of fingers with ulcers of vascular origin distal to the proximal interphalangeal joints), score on the Health Assessment Questionnaire–Disability Index (HAQ-DI)[29] and score on the Functional Assessment of Chronic Illness Therapy (FACIT)–Dyspnea questionnaire[30] at week 52; and the time to death from any cause (analyzed over the entire trial period). Scores on the HAQ-DI range from 0 to 3, with higher scores indicating worse disability. The minimal clinically important difference in HAQ-DI score in patients with diffuse cutaneous systemic sclerosis has been estimated to be 0.10 to 0.14.[31] The raw score on the FACIT-Dyspnea questionnaire ranges from 0 to 30 and the scaled score from 27.7 to 75.9, with higher scores indicating worse dyspnea; no minimal clinically important difference has been established for this tool. We also assessed categorical declines in FVC (the percentages of patients who had absolute declines from baseline in FVC of >5 and >10 percentage points of the predicted value at week 52 and the percentages of patients who had relative declines from baseline in FVC [measured in milliliters] of >5% and >10% at week 52) as end points for response to intervention.

For the lung function end points listed above, spirometry was performed at baseline and at weeks 2, 4, 6, 12, 24, 36, and 52. Spirometers were provided by the sponsor. Spirometry was performed in accordance with international guidelines.[32] The results were confirmed by personnel at a central reading center. The assessments of the modified Rodnan skin score were conducted at baseline and at weeks 12, 24, 36, and 52. The SGRQ, HAQ-DI, and FACIT-Dyspnea questionnaire were completed at baseline and at weeks

24 and 52. Safety was assessed from the first dose to 28 days after the last dose of the trial drug or placebo; assessments included clinical evaluation, laboratory measurements, and the recording of adverse events, coded according to the *Medical Dictionary for Regulatory Activities*, version 21.1.

### STATISTICAL ANALYSIS

All analyses were conducted in the patients who received at least one dose of the trial drug or placebo. The primary end point was analyzed with the use of a random-coefficient regression model (with random slopes and intercepts) that included effects of treatment, antitopoisomerase I antibody status (positive or negative), age, height, sex, baseline FVC (measured in milliliters), time, and treatment-by-time and baseline-by-time interactions. The slope of the decline in FVC was calculated for every patient, and the average was compared between trial groups. The analysis was based on all measurements taken over a 52-week period, including those from patients who discontinued the trial drug or placebo. The model allowed for missing data, with the assumption that the data were missing at random. Sensitivity analyses, including those in which we used the approach of multiple imputation for missing data, and the statistical analysis of other end points are described in sections D and E, respectively, in the Supplementary Appendix. The primary and secondary end points were tested under a hierarchical test strategy that protected the type I error (see section F in the Supplementary Appendix).[22] Significance tests were two-sided, with an alpha value of 0.05. The 95% confidence intervals for the end points that were not covered by the hierarchical testing procedure were not adjusted for multiplicity. Descriptive statistics are presented for safety data.

In the calculation of the sample size, the difference in the absolute change from baseline in FVC at week 52 between the trial groups was assumed to be 70 to 110 ml, which reflects a reduction of approximately 50% on the basis of the results of SLS-I[7] and the phase 3 INPULSIS trials involving patients with idiopathic pulmonary fibrosis[11] (in the absence of more appropriate data from placebo groups). No assumptions were made with regard to the potential effect of concomitant immunosuppressive therapy. A sample size of 260 patients per trial group was estimated to provide the trial 90% power to detect a between-group difference of 70 ml in the annual rate of decline in FVC, with the assumption of a standard deviation of 245 ml in both groups.

## RESULTS

### PATIENTS

A total of 576 patients received at least one dose of nintedanib or placebo (Fig. 1). The baseline characteristics of the patients were similar between trial groups (Table 1; and see section G in the Supplementary Appendix). Approximately half the patients had diffuse cutaneous systemic sclerosis, and half had limited cutaneous systemic sclerosis (51.9% and 48.1%, respectively). The median time since the onset of the first non-Raynaud's symptom was 3.4 years. The mean (±SD) age of the patients was 54.0±12.2 years, and the mean FVC and $DL_{CO}$ were 72.5±16.7% and 53.0±15.1% of the predicted value, respectively. The mean extent of fibrosis on high-resolution computed tomography was 36.0±21.3%. Almost half (48.4%) of the patients were receiving mycophenolate at baseline.

Among the patients who received at least one dose, 232 (80.6%) in the nintedanib group and 257 (89.2%) in the placebo group completed the 52-week intervention, and FVC measurements at week 52 were available for 241 (83.7%) and 257 (89.2%) patients, respectively. The mean duration of exposure to the trial drug or placebo from the first dose to week 52 (or to last dose in patients who discontinued the intervention before week 52) was 10.5±3.4 months in the nintedanib group and 11.4±2.4 months in the placebo group.

### PRIMARY END POINT AND SECONDARY LUNG FUNCTION END POINTS

The adjusted annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (–52.4 ml per year vs. –93.3 ml per year; difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P=0.04) (Fig. 2 and Table 2). Multiple-imputation sensitivity analyses for missing data yielded P values ranging from 0.06 to 0.10 (see section D in the Supplementary Appendix).

The curves for the change from baseline in FVC separated by week 12 and continued to diverge (Fig. 2C). The adjusted mean absolute change from baseline in FVC at week 52 was consistent with the result of the primary analysis: –54.6 ml in the nintedanib group and –101.0 ml

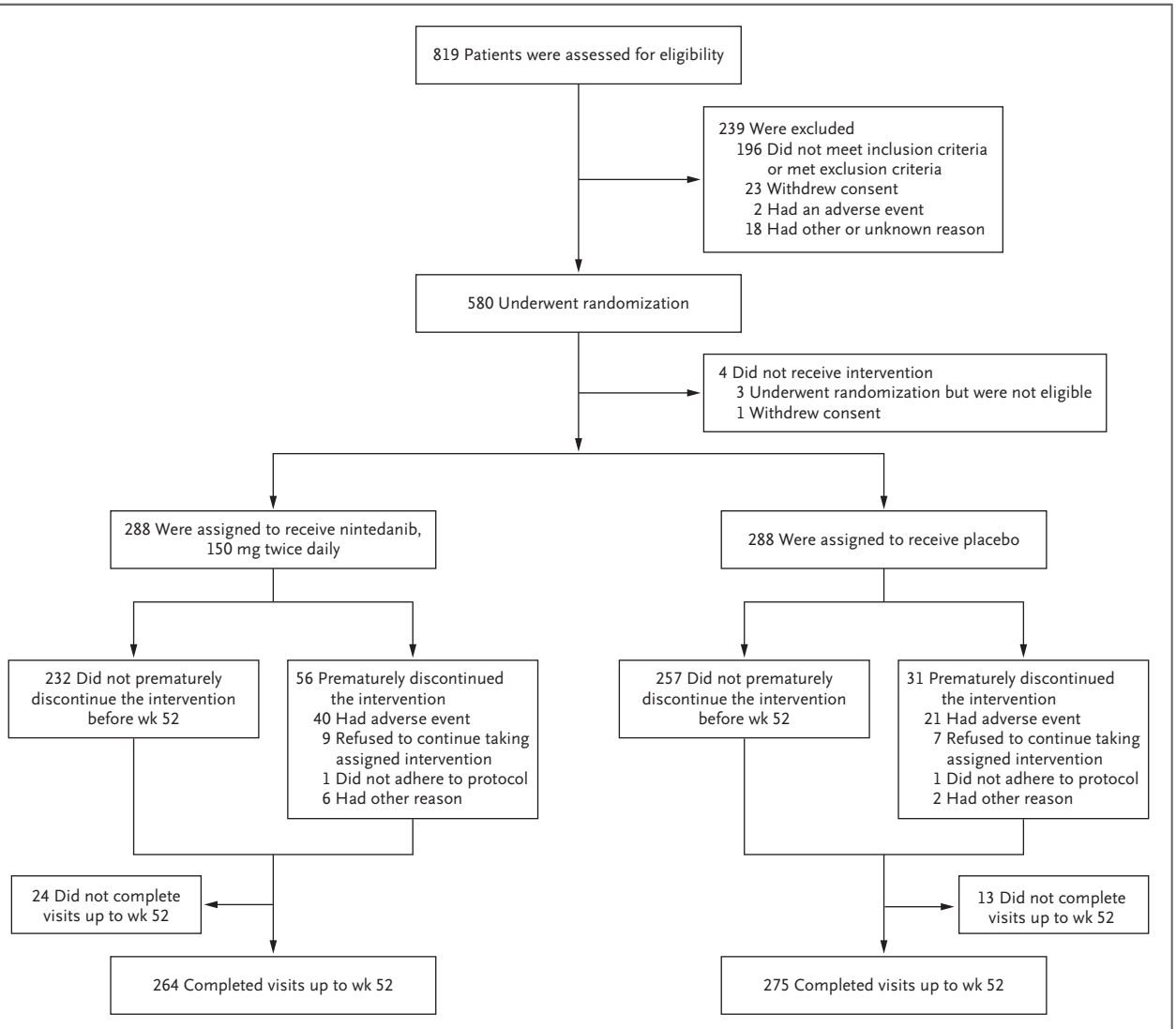


**Figure 1. Enrollment, Randomization, and Follow-up.**

in the placebo group (difference, 46.4 ml; 95% CI, 8.1 to 84.7) (Fig. 2 and Table 2). The adjusted mean annual rate of change in FVC as a percentage of the predicted value at week 52 was –1.4% in the nintedanib group and –2.6% in the placebo group (difference, 1.2 percentage points; 95% CI, 0.1 to 2.2) (Table 2). The percentages of patients who had an absolute decline from baseline in FVC of more than 5 percentage points of the predicted value at week 52 were 20.6% in the nintedanib group and 28.5% in the placebo group (odds ratio, 0.65; 95% CI, 0.44 to 0.96). The percentages of patients with a relative decline in FVC (measured in milliliters) of more than 10% at week 52 were 16.7% in the nintedanib group and 18.1% in the placebo group (odds ratio, 0.91; 95% CI, 0.59 to 1.41). A forest plot of prespecified subgroups, along with the P values for the treatment-by-time-by-subgroup interactions, is shown in section H in the Supplementary Appendix. The annual rates of change in FVC among the patients who were receiving mycophenolate at baseline were –40.2 ml per year in the nintedanib group and –66.5 ml per year in the placebo group, and the corresponding rates among the patients who were not receiving mycophenolate at baseline were –63.9 ml per year and –119.3 ml per year.

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Nintedanib (N=288) | Placebo (N=288) |
|---|---|---|
| Female sex — no. (%) | 221 (76.7) | 212 (73.6) |
| Age — yr | 54.6±11.8 | 53.4±12.6 |
| Diffuse cutaneous systemic sclerosis — no. (%) | 153 (53.1) | 146 (50.7) |
| Years since the onset of the first non-Raynaud's symptom | | |
| Median | 3.4 | 3.5 |
| Range | 0.3–7.1 | 0.4–7.2 |
| Extent of fibrosis of the lungs on high-resolution CT — % | 36.8±21.8 | 35.2±20.7 |
| FVC — ml | 2459±736 | 2541±816 |
| FVC — % of predicted value | 72.4±16.8 | 72.7±16.6 |
| $DL_{CO}$ — % of predicted value† | 52.9±15.1 | 53.2±15.1 |
| Antitopoisomerase antibody positive — no. (%)‡ | 173 (60.1) | 177 (61.5) |
| Modified Rodnan skin score§ | 11.3±9.2 | 10.9±8.8 |
| Patients with diffuse cutaneous systemic sclerosis | 17.0±8.7 | 16.3±8.9 |
| Patients with limited cutaneous systemic sclerosis | 4.9±4.2 | 5.4±4.1 |
| Total score on the SGRQ¶ | 40.7±20.2 | 39.4±20.9 |
| Score on the HAQ-DI‖ | 0.65±0.70 | 0.55±0.58 |
| Scaled score on the FACIT-Dyspnea questionnaire** | 47.01±9.64 | 45.67±9.90 |
| Receiving mycophenolate — no. (%) | 139 (48.3) | 140 (48.6) |
| Receiving methotrexate — no. (%) | 23 (8.0) | 15 (5.2) |

* Plus–minus values are means ±SD. Data on some variables were not available for all patients. A larger table of baseline characteristics is included in section G in the Supplementary Appendix. CT denotes computed tomography, $DL_{CO}$ diffusion capacity of the lungs for carbon monoxide, FACIT Functional Assessment of Chronic Illness Therapy, FVC forced vital capacity, HAQ-DI Health Assessment Questionnaire–Disability Index, and SGRQ St. George's Respiratory Questionnaire.

† The $DL_{CO}$ value was corrected for the hemoglobin level. $DL_{CO}$ values were available for 285 patients in the nintedanib group and 284 patients in the placebo group.

‡ Historical information on antitopoisomerase antibody status was used, or, if this information was not available to the trial sites, it was provided by a central laboratory.

§ The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis. Scores were available for 288 patients in the nintedanib group and 286 patients in the placebo group. Among the patients with diffuse cutaneous systemic sclerosis, scores were available for 153 of those in the nintedanib group and for 144 of those in the placebo group. Among the patients with limited cutaneous systemic sclerosis, scores were available for 135 of those in nintedanib group and for 142 of those in placebo group.

¶ Total scores on the SGRQ range from 0 to 100, with higher scores indicating worse health-related quality of life. Scores were available for 282 patients in the nintedanib group and 283 patients in the placebo group.

‖ Scores on the HAQ-DI range from 0 to 3, with higher scores indicating worse disability. Scores were available for 283 patients in the nintedanib group and 281 patients in the placebo group.

** Scaled scores on the FACIT-Dyspnea questionnaire range from 27.7 to 75.9, with higher scores indicating worse dyspnea. Scores were available for 283 patients in the nintedanib group and 285 patients in the placebo group.

### KEY SECONDARY END POINTS

The adjusted mean absolute change from baseline in modified Rodnan skin score at week 52 was –2.17 in the nintedanib group and –1.96 in the placebo group (difference, –0.21; 95% CI; –0.94 to 0.53). The adjusted mean absolute change from baseline in total score on the SGRQ at week 52 was 0.81 in the nintedanib group and –0.88 in the placebo group (difference, 1.69; 95% CI, –0.73 to 4.12). Prespecified subgroup analyses showed that the results for the key secondary end points did not differ significantly among the patients with different baseline characteristics (P>0.05 for the treatment-by-visit-by-subgroup interactions), as shown in sections I and J in the Supplementary Appendix.

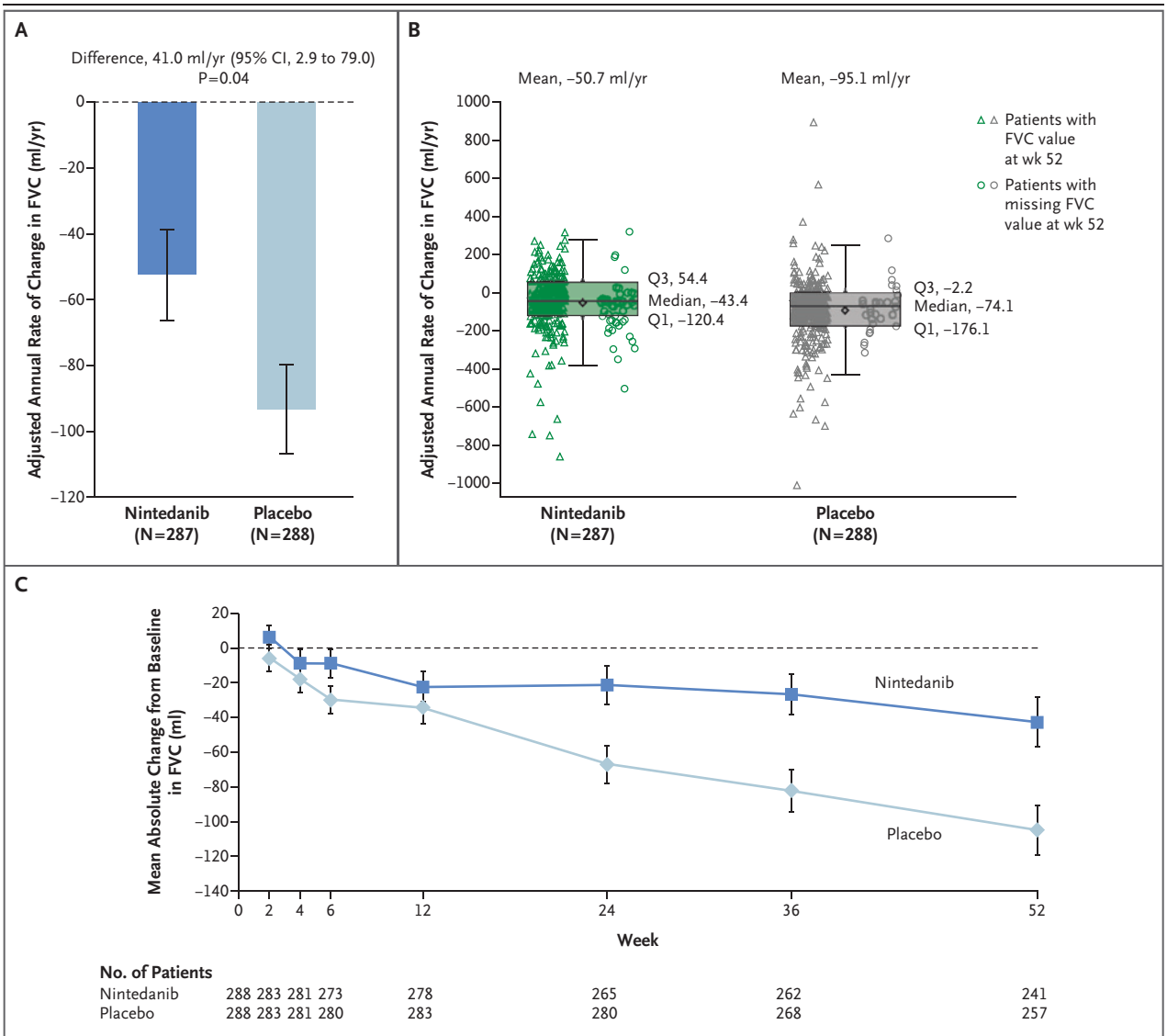


**Figure 2. Decline in Forced Vital Capacity.**

Panel A shows the between-group adjusted difference in the annual rate of decline in forced vital capacity (FVC) over 52 weeks. I bars indicate the standard error. Panel B shows box and whisker plots of the adjusted annual rates of decline in FVC over 52 weeks (based on rates calculated from the primary model for each patient) in the nintedanib group and the placebo group. Q1 denotes the first quartile, and Q3 the third quartile. The whiskers are drawn from the box to the most extreme point that is less than or equal to 1.5 times the interquartile range. The means differ slightly from the mean adjusted rates by treatment group estimated from the primary model shown in Panel A because of differences in covariate adjustment and handling of missing data. Panel C shows the observed change from baseline over time in FVC. I bars indicate the standard error.

### HAQ-DI and FACIT-Dyspnea Score

The difference in the absolute change from baseline in the score on the HAQ-DI at week 52 between the nintedanib group and the placebo group was 0.032 (95% CI, −0.035 to 0.099). The difference in the absolute change from baseline in the FACIT-Dyspnea score at week 52 between trial groups was 0.64 (95% CI, −0.51 to 1.79) (see section K in Supplementary Appendix).

### Adverse Events

The percentages of patients with any adverse event and any serious adverse event were similar in the nintedanib group and the placebo group

**Table 2. Primary and Secondary Efficacy End Points.***

| End Point | Nintedanib | Placebo | Difference (95% CI) |
|---|---|---|---|
| **Primary end point** | | | |
| Annual rate of decline in FVC assessed over 52 weeks — ml/yr | −52.4±13.8 | −93.3±13.5 | 41.0 (2.9 to 79.0)† |
| **Key secondary end points** | | | |
| Absolute change from baseline in modified Rodnan skin score at week 52 | −2.17±0.27 | −1.96±0.26 | −0.21 (−0.94 to 0.53)‡ |
| Absolute change from baseline in total score on the SGRQ at week 52 | 0.81±0.88 | −0.88±0.87 | 1.69 (−0.73 to 4.12)§ |
| **Other secondary end points** | | | |
| Absolute change from baseline in FVC at week 52 — ml | −54.6±13.9 | −101.0±13.6 | 46.4 (8.1 to 84.7)§ |
| Annual rate of decline in FVC — % of predicted value | −1.4±0.4 | −2.6±0.4 | 1.2 (0.1 to 2.2)§ |
| Absolute change from baseline in $DL_{CO}$ at week 52 — % of predicted value | −3.21±0.54 | −2.77±0.54 | −0.44 (−1.94 to 1.06)§ |
| Absolute change from baseline in net digital ulcer burden at week 52 | 0.03±0.05 | 0.06±0.04 | −0.03 (−0.16 to 0.09)§ |
| Patients with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 — no./total no. (%) | 59/287 (20.6) | 82/288 (28.5) | 0.65 (0.44 to 0.96)§¶ |
| Patients with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 — no./total no. (%) | 20/287 (7.0) | 24/288 (8.3) | 0.82 (0.44 to 1.52)§¶ |
| Patients with a relative decline from baseline in FVC, measured in milliliters, of >5% at week 52 — no./total no. (%) | 95/287 (33.1) | 125/288 (43.4) | 0.65 (0.46 to 0.91)§¶ |
| Patients with a relative decline from baseline in FVC, measured in milliliters, of >10% at week 52 — no./total no. (%) | 48/287 (16.7) | 52/288 (18.1) | 0.91 (0.59 to 1.41)§¶ |

* Changes from baseline are adjusted means ±SE based on the statistical models. Data on some variables were not available for all patients. FVC end points were analyzed in 287 patients in the nintedanib group and 288 patients in the placebo group, except for the absolute change from baseline in FVC in milliliters, which was analyzed in 288 patients in both groups. Modified Rodnan skin score was analyzed in 288 patients in the nintedanib group and 286 patients in the placebo group, total score on the SGRQ in 282 and 283 patients, $DL_{CO}$ in 285 and 284 patients, and net digital ulcer burden (the number of fingers with ulcers of vascular origin distal to the proximal interphalangeal joints) in 288 patients in both groups.
† P=0.04.
‡ P=0.58.
§ The 95% confidence interval was not adjusted for multiple comparisons.
¶ The difference was assessed as an odds ratio.

(Table 3). The percentage of patients who had an adverse event that led to the discontinuation of the assigned intervention was higher in the nintedanib group than in the placebo group (16.0% vs. 8.7%). The most common adverse event was diarrhea, which was reported in 75.7% of the patients in the nintedanib group and in 31.6% of the patients in the placebo group. Among the nintedanib-treated patients who had an adverse event of diarrhea, 49.5% had events that were classified as mild (at worst) in intensity and 45.0% had events that were classified as moderate (at worst). Elevations in alanine aminotransferase level, aspartate aminotransferase level, or both to at least three times the upper limit of the normal range were reported in 4.9% of the patients in the nintedanib group and in 0.7% of those in the placebo group. No patients met criteria for Hy's law (serum alanine aminotransferase or aspartate aminotransferase level of more than three times the upper limit of the normal range and bilirubin level of more than two times the upper limit of the normal range without an identifiable cause).

### MORTALITY

Over the entire trial period, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died (hazard ratio, 1.16; 95% CI, 0.47 to 2.84). Causes of death are listed in section L in the Supplementary Appendix.

## DISCUSSION

The SENSCIS trial was a large randomized, double-blind trial involving patients with ILD associated with systemic sclerosis. The results showed that the rate of decline in FVC over 52

**Table 3. Adverse Events.***

| Event | Nintedanib (N=288) | Placebo (N=288) |
|---|---|---|
| | *no. of patients (%)* | |
| Any adverse event | 283 (98.3) | 276 (95.8) |
| Most common adverse events† | | |
| Diarrhea | 218 (75.7) | 91 (31.6) |
| Nausea | 91 (31.6) | 39 (13.5) |
| Skin ulcer | 53 (18.4) | 50 (17.4) |
| Vomiting | 71 (24.7) | 30 (10.4) |
| Cough | 34 (11.8) | 52 (18.1) |
| Nasopharyngitis | 36 (12.5) | 49 (17.0) |
| Upper respiratory tract infection | 33 (11.5) | 35 (12.2) |
| Abdominal pain | 33 (11.5) | 21 (7.3) |
| Fatigue | 31 (10.8) | 20 (6.9) |
| Weight decrease | 34 (11.8) | 12 (4.2) |
| Severe adverse event‡ | 52 (18.1) | 36 (12.5) |
| Serious adverse event§ | 69 (24.0) | 62 (21.5) |
| Fatal adverse event | 5 (1.7) | 4 (1.4) |
| Adverse event leading to discontinuation of the intervention | 46 (16.0) | 25 (8.7) |

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.
† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.
‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.
§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

weeks among patients with ILD associated with systemic sclerosis was lower for those who received nintedanib than for those who received placebo. Sensitivity analyses of this end point based on multiple imputation for missing data yielded P values ranging from 0.06 to 0.10. Systemic sclerosis–associated ILD has a variable course, but many patients with this condition have progression of disease, with a decline in FVC that is associated with death.[33-35] Although the annual rate of decline in FVC among the patients who received placebo in our trial was lower than that observed among the patients with idiopathic pulmonary fibrosis who received placebo in the INPULSIS trials[11] (–93.3 ml in our trial vs. –223.5 ml in the INPULSIS trials), the relative effect of nintedanib as compared with placebo on reducing the rate of decline in FVC was similar (44% vs. 49%, respectively). In our trial and SLS-I,[7] the difference between active treatment and placebo in the observed change from baseline in FVC as a percentage of the predicted value were in the same range. The absolute between-group difference in the annual rate of decline in FVC observed in our trial (41 ml in favor of the nintedanib group) was smaller than assumed in the sample-size calculation. We speculate that this was because approximately half of the trial population were receiving mycophenolate at baseline and approximately half had limited cutaneous systemic sclerosis. This resulted in a trial population in which the decline in FVC in the placebo group was lower than assumed on the basis of historical data. The decline in FVC in the placebo group, as well as the magnitude of the effect of nintedanib, differed depending on mycophenolate use. Despite the large variability associated with the adjusted annual rates of decline in FVC observed in the current trial and the limitations inherent in comparing groups of patients who had not undergone randomization according to mycophenolate use, these data suggest a potential benefit of mycophenolate on lung function.

The SENSCIS trial involved a broad range of patients with ILD associated with systemic sclerosis, making the results relevant for the majority of patients with this condition. However, because we excluded patients with clinically significant pulmonary hypertension, our data cannot be applied to such patients. The lower rate of decline in FVC in the nintedanib group was not accompanied by a benefit with respect to health-related quality of life. No treatment effect was observed with respect to skin fibrosis, as assessed with the use of the modified Rodnan skin score. The modified Rodnan skin score improved in both trial groups, reflecting the natural course of skin fibrosis in patients with systemic sclerosis a few years after the onset of disease. Although training was provided to all investigators, the limitations of the modified Rodnan skin score as a semiquantitative end point in large international trials should also be considered. No effect of nintedanib was observed with respect to patient-reported outcomes. Thus, while

the results of the current trial suggest that nintedanib is effective in reducing the decline in FVC in patients with ILD associated with systemic sclerosis, this trial does not support nintedanib as a disease-modifying agent for systemic sclerosis as a whole (i.e., nintedanib does not address other organ complications).

The safety and adverse-event profile of nintedanib in the SENSCIS trial was similar to profiles observed in the INPULSIS trials,[11] although, as might be expected, gastrointestinal adverse events were more common in patients with ILD associated with systemic sclerosis than in those with idiopathic pulmonary fibrosis in both the active-drug and placebo groups. Although the percentage of patients who discontinued the assigned intervention because of adverse events was higher in the nintedanib group than in the placebo group, the percentage of those who discontinued the assigned intervention because of adverse events was lower in the current trial than in the INPULSIS trials[11] and more than 80% of the patients continued to receive nintedanib for 52 weeks. Given the potential adverse effects that vascular endothelial growth factor receptor inhibitors have on wound healing,[36] we note that there was no between-group difference in net digital ulcer burden.

In conclusion, the results of the SENSCIS trial showed that nintedanib has a beneficial effect by reducing the rate of decline in FVC in patients with ILD associated with systemic sclerosis over a 1-year period. In this trial, no other clinical benefit was observed. An uncontrolled open-label extension study (ClinicalTrials.gov number, NCT03313180) is ongoing and will provide long-term data on nintedanib therapy in patients with ILD associated with systemic sclerosis.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by Boehringer Ingelheim.

Dr. Distler reports receiving grant support and lecture fees from Actellion, fees for project scoring from AbbVie, consulting fees from Acceleron Pharma, Anamar, Amgen, Blade Therapeutics, CSL Behring, ChemomAb, Ergonex, Glenmark Pharma, GSK, Inventiva, Italfarmaco, iQvia, Medac, Medscape, Lilly, Sanofi, Target BioScience, and UCB, grant support, consulting fees, and lecture fees from Bayer and Boehringer Ingelheim, fees for an interview from Catenion, lecture fees from iQone, Menarini, Mepha, and Novartis, grant support and consulting fees from Mitsubishi, lecture fees and consulting fees from MSD and Roche, and lecture fees, consulting fees, and travel support from Pfizer, and holding patent US8247389 on the treatment of systemic sclerosis, assigned to the University of Zurich; Dr. Highland, receiving grant support and lecture fees from and serving on an advisory committee for Actelion Pharmaceuticals, receiving lecture fees from Bayer Healthcare, receiving grant support, lecture fees, and consulting fees from and serving on a steering committee for Boehringer Ingelheim, serving as a site principal investigator for Genentech, Eiger Pharmaceuticals, and Reata Pharmaceuticals, and receiving grant support and lecture fees from United Therapeutics; Dr. Gahlemann, being employed by Boehringer Ingelheim; Dr. Azuma, receiving lecture fees and consulting fees from Boehringer Ingelheim, lecture fees from Shionogi, and consulting fees from Taiho Pharmaceuticals and Asahikasei Pharma; Dr. Fischer, receiving consulting fees, fees for serving on a steering committee, and fees for serving as principal investigator from Genentech-Roche and consulting fees from Pfizer and Genentech; Dr. Mayes, receiving advisory board fees from Galapagos NV Pharma, Astellas, and Mitsubishi-Tanabe, lecture fees from Medtelligence, fees for serving as a reviewer for a grant program from Actellion Pharma, and grant support from Bayer, Reata, Sanofi, Corbus, and Eicos/Sciences; Dr. Raghu, receiving consulting fees from Bellerophan, Biogen, and Genentech-Roche, serving as a consultant for BMS, Fibrogen, Gilead, Nitto, and Promedior, receiving consulting fees and travel support from Revistan, Sanofi, and Veracyte, and receiving consulting fees from and serving as chair of a data and safety monitoring board for Avalyn; Drs. Sauter, Girard, Alves, Clerisme-Beaty, Stowasser, and Tetzlaff, being employed by Boehringer Ingelheim; Dr. Kuwana, receiving fees for serving on a steering committee, consulting fees, and fees for serving on a speakers bureau from Chugai, grant support and fees for serving on a speakers bureau from Actellion, and consulting fees from Reata, Bayer, Corbus, and CSL Behring; and Dr. Maher, receiving grant support, consulting fees, and fees for serving on data and safety monitoring committees from GlaxoSmithKline, grant support and consulting fees from UCB, consulting fees from Apellis, AstraZeneca, Bayer, Biogen Idec, Galapagos, Indalo, Pliant, ProMetic, Samumed, and Galecto, and consulting fees and lecture fees from Boehringer Ingelheim and Roche. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial; Veronika Kohlbrenner of Boehringer Ingelheim Pharmaceuticals for her advice on the interpretation of safety data; Elizabeth Ng and Wendy Morris of FleishmanHillard Fishburn, London, for medical writing assistance (supported financially by Boehringer Ingelheim) during the preparation of an earlier version of the manuscript; the following representatives of scleroderma patient organizations for their advice regarding aspects of the design and implementation of this clinical trial: Edith Brown (Scleroderma and Raynaud's U.K.), Ilaria Galetti (Federation of European Scleroderma Associations [FESCA] and Gruppo Italiano per la Lotta alla Sclerodermia, Italy), Alex Gonzalez (Scleroderma Research Foundation, United States), Alexandra Paula Portales Guiraud (Asociación Española de Esclerodermia, Spain), Ann Tyrrell Kennedy (FESCA), Catarina Leite (Associação Portuguesa de Doentes com Esclerodermia, Portugal), Michael Oeschger (Sklerodermie Selbsthilfe e.V., Germany), Robert J. Riggs (Scleroderma Foundation, United States), Annelise Rønnow (FESCA and Sklerodermiforeningen, Denmark), Maureen Sauvé (Scleroderma Canada), and Joep Welling (FESCA); and the members of the Data Monitoring Committee (James R. Seibold [chair], Ulrich Costabel, Robert Makuch, and Timothy Shapiro) and the Adjudication Committee (Lorcan McGarvey [chair], Murat İnanç, Alan B Miller, Scott Kasner, and Bradley Knight). We acknowledge general support to Dr. Maher from the National Institute for Health Research (NIHR Clinician Scientist Fellowship) and the British Lung Foundation (British Lung Foundation Chair in Respiratory Research). See also section M of the Supplementary Appendix.

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