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Effect of Nintedanib on Lung Function in Patients With Systemic Sclerosis–Associated Interstitial Lung Disease: Further Analyses of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. In the SENSCIS trial in subjects with systemic sclerosis–associated interstitial lung disease (SSc-ILD), nintedanib reduced the rate of decline in forced vital capacity (FVC) over 52 weeks by 44% versus placebo. This study was undertaken to investigate the effects of nintedanib on categorical changes in FVC and other measures of ILD progression.

Methods. In post hoc analyses, we assessed the proportions of subjects with categorical changes in FVC % predicted at week 52 and the time to absolute decline in FVC of ≥5% predicted or death and absolute decline in FVC of ≥10% predicted or death.

Results. A total of 288 subjects received nintedanib and 288 subjects received placebo. At week 52, in subjects treated with nintedanib and placebo, respectively, 55.7% and 66.3% had any decline in FVC % predicted, 13.6% and 20.1% had a decline in FVC of >5% to ≤10% predicted, and 3.5% and 5.2% had a decline in FVC of >10% to ≤15% predicted; 34.5% and 43.8% had a decrease in FVC of ≥3.3% predicted (proposed minimal clinically important difference [MCID] for worsening of FVC), while 23.0% and 14.9% had an increase in FVC of ≥3.0% predicted (proposed MCID for improvement in FVC). Over 52 weeks, the hazard ratio (HR) for an absolute decline in FVC of ≥5% predicted or death with nintedanib versus placebo was 0.83 (95% confidence interval [95% CI] 0.66–1.06) (P = 0.14), and the HR for an absolute decline in FVC of ≥10% predicted was 0.64 (95% CI 0.43–0.95) (P = 0.029).

Conclusion. These results suggest that nintedanib has a clinically relevant benefit on the progression of SSc-ILD.

INTRODUCTION

Systemic sclerosis (SSc) is a rare and heterogeneous autoimmune disease characterized by microvascular damage and progressive fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common manifestation of SSc and the leading cause of death in subjects with SSc (2). The course of SSc-associated ILD (SSc-ILD) is unpredictable, but a decline in forced

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vital capacity (FVC) in subjects with SSc-ILD is an indicator of ILD progression and is associated with mortality (3–7). While there is no established definition for progression of ILD, in 2015, the Outcome Measures in Rheumatology (OMERACT) connective tissue disease–associated ILD (CTD-ILD) Working Group agreed that a relative decline in FVC % predicted of ≥10%, or a relative decline in FVC % predicted of ≥5% to <10% with a relative decline in diffusing capacity for carbon monoxide (DL_{CO}) % predicted ≥15%, represents clinically meaningful progression of SSc-ILD (8).

Nintedanib, an intracellular inhibitor of tyrosine kinases (9), has been approved in many countries for the treatment of idiopathic pulmonary fibrosis (IPF) and SSc-ILD. Clinical trials in subjects with IPF (INPULSIS) (10), with SSc-ILD (SENSCIS) (11), and with various forms of progressive fibrosing ILDs (INBUILD) (12), including progressive autoimmune disease-related ILDs (13), have shown that nintedanib reduces the rate of decline in FVC (milliliters/year). The objective of the current analyses was to investigate the effects of nintedanib on categorical changes in FVC and other measures of ILD progression in subjects with SSc-ILD in the SENSCIS trial.

PATIENTS AND METHODS

Trial design. The design of the SENSCIS trial (ClinicalTrials.gov identifier: NCT02597933) has been published previously, together with the trial protocol (11). Briefly, eligible subjects had SSc with onset of first non–Raynaud's phenomenon symptom <7 years before screening, extent of fibrotic ILD ≥10% on a high-resolution computed tomography (HRCT) scan (based on assessment of the whole lung), FVC ≥40% predicted, and DL_{CO} of the lung (corrected for hemoglobin) 30–89% predicted. Subjects receiving prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate. Spirometers were provided to the sites and the results were confirmed centrally. Spirometry was performed in accordance with guidelines issued by the American Thoracic Society and European Respiratory Society (14), including daily calibration of the spirometer. Percent predicted values for FVC were calculated using the Global Lung Initiative equations based on the subject's age, sex, race, and height (15). The method used to measure DL_{CO} and the equation used to calculate percent predicted values for DL_{CO} were chosen by the site.

Subjects were randomized 1:1 to receive nintedanib 150 mg twice a day or placebo, stratified by the presence of anti–topoisomerase I (anti–topo I) antibodies. Subjects could continue to receive treatment in a blinded manner until the last subject had reached week 52, but for ≤100 weeks. Subjects who discontinued treatment prematurely were asked to remain in the trial and attend visits as originally planned. The trial was conducted in accordance with the trial protocol, the principles of the Declaration of Helsinki, and the International Council for Harmonisation Guidelines for Good Clinical Practice, and was approved by local authorities. All subjects provided written informed consent.

End points. The following were assessed in the nintedanib and placebo groups based on data at week 52: the proportion of subjects with categorical absolute declines or increases in FVC % predicted or categorical relative declines or increases in FVC (milliliters) (as listed in the Results section); the proportion of subjects who met proposed thresholds for minimal clinically important differences (MCID) for improvement in FVC (absolute increase of ≥3.0% predicted), stable FVC (absolute increase of <3.0% predicted or decrease of <3.3% predicted), and worsening of FVC (absolute decrease of ≥3.3% predicted) based on data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Study Short Form-36 (16); and time to 1) an absolute decline in FVC of ≥5% predicted or death; 2) an absolute decline in FVC of ≥10% predicted or death; and 3) an absolute decline in FVC of ≥10% predicted or absolute decline in FVC of ≥5% to <10% predicted with an absolute decline in DL_{CO} of ≥15% predicted, or death. The proportions of subjects who met proposed thresholds for improvement in FVC, stable FVC, and worsening of FVC at week 52 were also assessed in subgroups defined by the following baseline characteristics: FVC of <80% versus ≥80% predicted, extent of fibrotic ILD on HRCT of <20% versus ≥20%, time since onset of first non–Raynaud's phenomenon symptom ≤3 versus >3 years, and glucocorticoid use.

Statistical analysis. Analyses were conducted post hoc in subjects who received ≥1 dose of trial medication (intention-to-treat). The proportions of subjects with categorical declines or increases in FVC % predicted and FVC measured in milliliters at week 52, and the proportions of subjects who met proposed thresholds for improvement in FVC, stable FVC, and worsening of FVC at week 52 were compared between treatment groups using a Cochran-Mantel-Haenszel test, stratified by anti–topo I antibody status. In the subgroup analyses, the proportions of subjects who met proposed thresholds for improvement in FVC, stable FVC, and worsening of FVC at week 52 were compared between treatment groups using a logistic regression model, including trial medication (nintedanib/placebo), anti–topo I antibody status, subgroup, and treatment-by-subgroup interaction as terms. Missing values were imputed using a worst value carried forward approach. Exploratory interaction *P* values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups. Time-to-event end points were analyzed based on data from 52 weeks (± 7 days) using a Cox regression model with a term for treatment and stratified by anti–topo I antibody status. Analyses were not adjusted for multiplicity. Hazard ratios (HRs) or odds ratios and 95% confidence intervals (95% CIs) were calculated.

RESULTS

Characteristics of the study subjects. A total of 576 subjects received ≥1 dose of trial medication (288 received nintedanib and 288 received placebo). The baseline

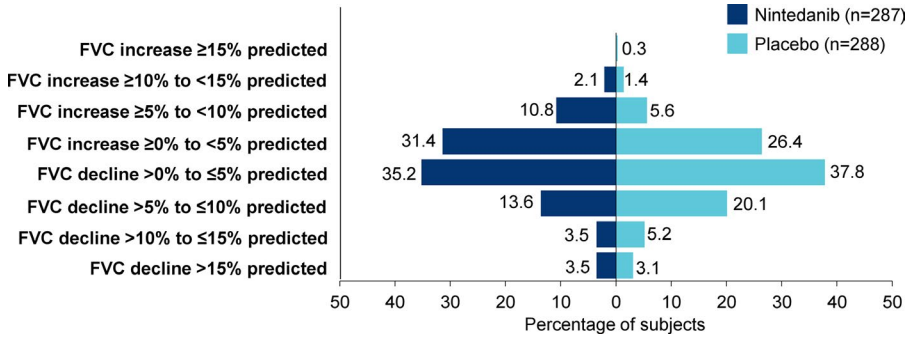

Figure 1. Proportions of subjects with systemic sclerosis–associated interstitial lung disease (SSc-ILD) treated with nintedanib or placebo in the SENSCIS trial who had the indicated absolute increases and declines in forced vital capacity (FVC) % predicted at week 52. A post-baseline FVC measurement was not available for 1 patient.

characteristics of subjects in the SENSCIS trial have been described previously (11). The mean ± SD age was 54.0 ± 12.2 years, 75.2% of subjects were female, and 67.2% were White. The mean ± SD FVC was 2,500 ± 777 milliliters and 72.5 ± 16.7 % predicted, and the mean ± SD DL_{CO} was 53.0 ± 15.1 % predicted. Baseline characteristics were similar between the treatment groups (11).

Categorical changes in FVC % predicted. In total, 46 subjects (16.0%) in the nintedanib group and 31 subjects (10.8%) in the placebo group had missing FVC data at week 52. At week 52, 55.7% of subjects in the nintedanib group and 66.3% of subjects in the placebo group had a decline in FVC % predicted. At week 52 the proportions of subjects in the nintedanib group with an absolute decline in FVC of >5% to ≤10% predicted and an absolute decline in FVC of >10% to ≤15% predicted were 13.6% and 3.5%, respectively, while the proportions of subjects in the placebo group with an absolute decline in FVC of >5% to ≤10% predicted and an absolute decline in FVC of >10% to ≤15% predicted were 20.1% and 5.2%, respectively (Figure 1). The proportions of subjects who met thresholds for relative declines or increases in FVC (in milliliters) are shown in Supplementary Figure 1 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41576/abstract). In the nintedanib and placebo groups, respectively, 34.5% versus 43.8% of subjects had an absolute decrease in FVC of ≥3.3% predicted at week 52 (the proposed MCID for worsening of FVC), while 23.0% versus 14.9% had an absolute increase in FVC of ≥3.0% predicted at week 52 (the proposed MCID for improvement in FVC) (Figure 2). Exploratory interaction *P* values did not indicate heterogeneity in the effect of nintedanib versus placebo between subgroups classified by FVC % predicted, extent of fibrotic ILD on HRCT, time since onset of first non–Raynaud's phenomenon symptom at baseline, or glucocorticoid

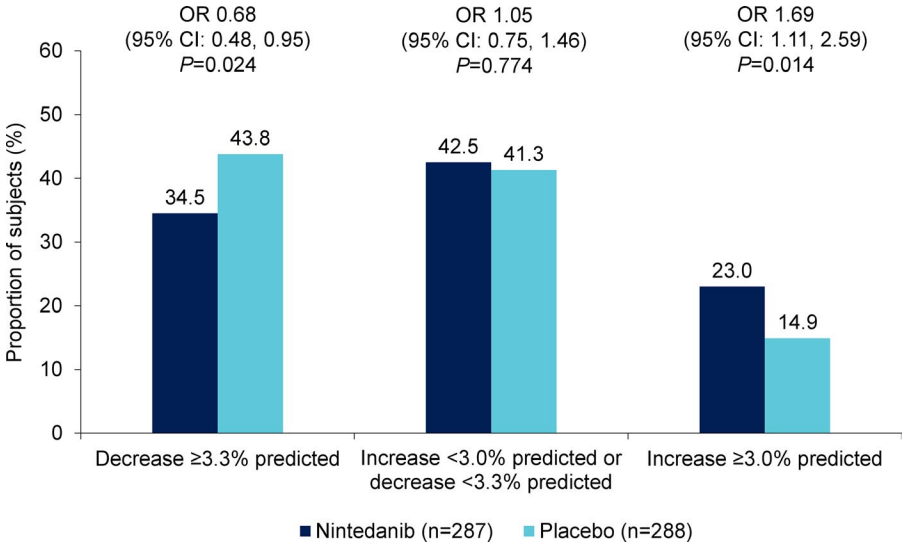

Figure 2. Proportions of subjects with SSc-ILD treated with nintedanib or placebo in the SENSCIS trial who met the proposed threshold for worsening of FVC (decrease of ≥3.3% predicted), stable FVC (increase of <3.0% predicted or decrease of <3.3% predicted), or improvement in FVC (increase of ≥3.0% predicted) at week 52. A post-baseline FVC measurement was not available for 1 patient. OR = odds ratio; 95% CI = 95% confidence interval (see Figure 1 for other definitions).

Table 1. Proportions of subjects with absolute declines in FVC % predicted or death over 52 weeks in the SENSCIS trial*

	Nintedanib (n = 288)	Placebo (n = 288)
Absolute decline in FVC ≥5% predicted or death		
Subjects with event, no. (%)	124 (43.1)	145 (50.3)
Hazard ratio (95% confidence interval)	0.83 (0.66–1.06)	
P	0.14	
Absolute decline in FVC ≥10% predicted or death		
Subjects with event, no. (%)	40 (13.9)	62 (21.5)
Hazard ratio (95% confidence interval)	0.64 (0.43–0.95)	
P	0.03	
Absolute decline in FVC ≥10% predicted or absolute decline in FVC ≥5% to <10% predicted with absolute decline in DLco ≥15% predicted, or death		
Subjects with event, no. (%)	39 (13.5)	69 (22.9)
Hazard ratio (95% confidence interval)	0.58 (0.39–0.87)	
P	0.008	

* FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide.

use (*P* > 0.05 for treatment-by-subgroup interactions) (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41576/abstract).

Time to lung function decline or death. Over 52 weeks, an absolute decline in FVC of ≥5% predicted or death occurred in 43.1% of the subjects in the nintedanib group and 50.3% of the subjects in the placebo group (HR 0.83 [95% CI 0.66–1.06]; *P* = 0.14), and an absolute decline in FVC of ≥10% predicted or death occurred in 13.9% of the subjects in the nintedanib group and 21.5% of the subjects in the placebo group (HR 0.64 [95% CI 0.43–0.95]; *P* = 0.029) (Table 1 and Figure 3). Over 52 weeks, an absolute decline in FVC of ≥10% predicted, absolute decline in FVC of ≥5% to <10% predicted with an absolute decline in DLco of ≥15% predicted, or death occurred in 13.5% and 22.9% of subjects in the nintedanib and placebo groups, respectively (HR 0.58 [95% CI 0.39–0.87]; *P* = 0.008) (Table 1).

DISCUSSION

These findings from the SENSCIS trial provide further evidence that nintedanib has a clinically relevant effect on the progression of SSc-ILD. Although there is no established definition for the progression of ILD, declines in FVC of >10% predicted have been used to assess the proportion of subjects with clinically relevant ILD progression in previous studies of SSc-ILD (6,7) and other ILDs (17–20), based on the association between decline in FVC and mortality. In addition, thresholds for improvement and worsening of FVC, derived based on anchoring to the health transition question from the Medical Outcomes Study Short Form-36 in the Scleroderma Lung Studies I and II, have been proposed as MCIDs at a population level (16). In a recent European Delphi consensus study, physicians experienced in the management of SSc-ILD agreed that the progression of SSc-ILD can be assessed using changes in % predicted values for FVC and DLco and that measurement of lung function is an effective tool in long-term follow-up of ILD progression in patients with SSc-ILD (21).

Several studies have shown that a decline in FVC is associated with mortality in patients with SSc-ILD. A study of 171 patients at a single center showed that patients who died within 4 years of SSc-ILD diagnosis had a higher annual rate of decline in FVC than those who died between 4 and 8 years after their SSc-ILD diagnosis or who survived for >8 years (22). Data from Scleroderma Lung Study I (n = 158) showed that absolute declines in FVC of ≥10%

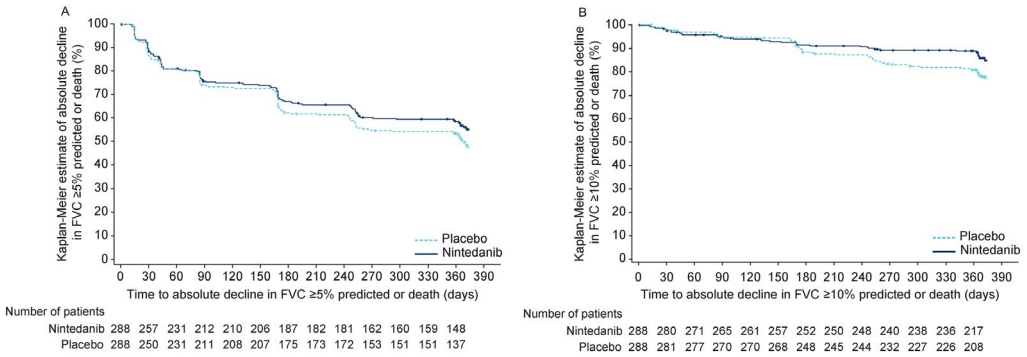

Figure 3. Time to **A**, absolute decline in FVC of ≥5% predicted or death and **B**, absolute decline in FVC of ≥10% predicted or death, over 52 weeks in patients with SSc-ILD treated with nintedanib or placebo in the SENSCIS trial. See Figure 1 for definitions.

predicted or DLco of ≥15% predicted over 2 years were associated with mortality over a median follow-up period of 8 years, while data from Scleroderma Lung Study II (n = 142) showed that an absolute decline in FVC of ≥10% predicted at 1 year was associated with mortality over a median follow-up period of 4 years (7). In a large cohort of subjects in the European Scleroderma Trials and Research (EUSTAR) database (n = 857), an absolute decline in FVC of ≥10% predicted, or an absolute decline in FVC of ≥5% predicted with a decline in DLco of ≥15% predicted, over 12 months was predictive of mortality over a maximum follow-up period of 5 years (5). Recent data from a well-characterized Norwegian cohort (n = 391) showed that ILD progression defined as severe (absolute decline in FVC of >10% predicted or decline in FVC of 5–10% predicted with decline in DLco of ≥15% predicted) or moderate (absolute decline in FVC of 5–10% predicted with decline in DLco of <15% predicted) over a mean follow-up period of almost 4 years was associated with lower survival compared with stable FVC (change <5% predicted), with 10-year survival rates of 59% versus 78% (6). In a long-term UK study of 162 patients, a relative decline in FVC (in milliliters) of ≥10%, or a relative decline in FVC (in milliliters) of 5–9% with a relative decline in DLco of >15% at 1 year was strongly associated with mortality over 15 years (4).

Subgroup analyses of the data from the SENSCIS trial suggest that the proportions of subjects who met proposed thresholds for worsening and improvement in FVC were consistent across subgroups based on FVC % predicted, time since onset of first non–Raynaud's phenomenon symptom, extent of fibrotic ILD on HRCT, and glucocorticoid use at baseline. Previous analyses have shown that the proportions of subjects who met these thresholds were similar across subgroups by anti–topo I antibody status (23), SSc subtype (limited versus diffuse cutaneous SSc) (24), and mycophenolate use at baseline (25). Taken together, these data support a benefit of nintedanib in reducing the proportion of patients with clinically relevant progression of ILD, and increasing the proportion of patients with stable or increased FVC, across a broad population of subjects with SSc-ILD, consistent with the effects of nintedanib previously demonstrated in patients with IPF (26–28).

Strengths of our study include the participation of a large number of well-characterized subjects with SSc-ILD and the highly standardized procedure used for measurement of FVC. Limitations of our analyses include that they were conducted post hoc and, as such, should be considered exploratory. The present study did not assess whether the categorical changes in FVC translated into meaningful improvements/declines in patient-reported outcomes. Our analyses were not adjusted for multiple testing or for confounding factors such as use of mycophenolate. The number of deaths was too small to enable associations between FVC decline and mortality to be studied.

In conclusion, these further analyses of FVC decline in the SENSCIS trial support a clinically meaningful effect of nintedanib on slowing the progression of SSc-ILD.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Maher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Maher, Mayes, Stock, Schoof, Alves, Raghu.
Acquisition of data. Maher, Mayes, Kreuter, Aringer, Castellvi, Cutolo.
Analysis and interpretation of data. Maher, Mayes, Kreuter, Volkmann, Aringer, Castellvi, Cutolo, Stock, Schoof, Alves, Raghu.

ROLE OF THE STUDY SPONSOR

Boehringer Ingelheim was involved in the design of the study, the interpretation of the data, and the writing of the manuscript. The authors had the final decision to submit the manuscript for publication. Writing assistance was provided by Julie Fleming and Wendy Morris (FleishmanHillard Fishburn, London, UK; supported financially by Boehringer Ingelheim).

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