## Title

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SHORT REPORT

# Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and risk factors for rapid progression

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## ABSTRACT

**Objective** To investigate the rate of decline in forced vital capacity (FVC), and the effect of nintedanib on the rate of decline in FVC, in subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD) who had risk factors for rapid decline in FVC.

**Methods** The SENSCIS trial enrolled subjects with SSc and fibrotic ILD of ≥10% extent on high-resolution CT. The rate of decline in FVC over 52 weeks was analysed in all subjects and in those with early SSc (<18 months since first non-Raynaud symptom), elevated inflammatory markers (C reactive protein ≥6 mg/L and/or platelets ≥330×$10^9$/L) or significant skin fibrosis (modified Rodnan skin score (mRSS) 15–40 or mRSS ≥18) at baseline.

**Results** In the placebo group, the rate of decline in FVC was numerically greater in subjects with <18 months since first non-Raynaud symptom (–167.8 mL/year), elevated inflammatory markers (–100.7 mL/year), mRSS 15–40 (–121.7 mL/year) or mRSS ≥18 (–131.7 mL/year) than in all subjects (–93.3 mL/year). Nintedanib reduced the rate of FVC decline across subgroups, with a numerically greater effect in patients with these risk factors for rapid FVC decline.

**Conclusion** In the SENSCIS trial, subjects with SSc-ILD who had early SSc, elevated inflammatory markers or extensive skin fibrosis had a more rapid decline in FVC over 52 weeks than the overall trial population. Nintedanib had a numerically greater effect in patients with these risk factors for rapid ILD progression.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Risk factors for more rapid progression of systemic sclerosis-associated interstitial lung disease (SSc-ILD) have been identified in several studies but need further validation.

### WHAT THIS STUDY ADDS

⇒ In the placebo group of the SENSCIS trial in patients with fibrosing SSc-ILD, the rate of decline in forced vital capacity (FVC) over 52 weeks was greater in patients with early disease, elevated inflammatory markers or extensive skin fibrosis at baseline.

⇒ Nintedanib had a numerically greater effect on reducing the rate of FVC decline in patients with these risk factors.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results support the prompt initiation of nintedanib in patients with fibrosing SSc-ILD to target pulmonary fibrosis and preserve lung function.

## INTRODUCTION

Systemic sclerosis (SSc) is a complex and heterogeneous autoimmune disease characterised by progressive fibrosis of the skin and internal organs. Interstitial lung disease (ILD) is a common manifestation of SSc and the leading cause of death in patients with SSc.[1] A decline in forced vital capacity (FVC) in patients with SSc-ILD is associated with an increased risk of mortality.[2 3] Although the course of SSc-ILD is variable,[2 4] risk factors for decline in FVC have been identified. These include short SSc duration,[5] male sex,[6] elevated inflammatory markers[7] and progression of skin fibrosis.[8] Diffuse cutaneous SSc (dcSSc) has been identified as a risk factor for decline in FVC in some but not all studies.[9 10]

Patients with diffuse SSc and risk factors for rapid progression of ILD are typically given immunosuppressants to address underlying inflammation. However, since inflammation and fibrosis can coexist early in the course of SSc-ILD, these patients may also benefit from antifibrotic therapy. Early treatment to stabilise lung function and improve outcomes

is an important aim of the management of SSc-ILD.[11] Recent studies have investigated the efficacy of particular therapies in patients with dcSSc and specific risk factors for progression of SSc-ILD, including early disease.[12–14]

Nintedanib is an intracellular inhibitor of tyrosine kinases that has antifibrotic and anti-inflammatory effects that inhibit pathways involved in fibrosis.[15] In the SENSCIS trial conducted in a broad population of subjects with SSc-ILD, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks versus placebo by an average of 44%.[16] In this post-hoc analysis, we investigated the rate of decline in FVC over 52 weeks, and the effect of nintedanib on the rate of decline in FVC, in subjects in the SENSCIS trial who had risk factors for rapid decline in FVC at baseline.

## METHODS

The design of the SENSCIS trial (NCT02597933) has been described, and the protocol is publicly available.[16] Briefly, subjects had SSc with their first non-Raynaud symptom in the prior ≤7 years, extent of fibrotic ILD on high-resolution CT ≥10% (based on assessment of the whole lung), FVC ≥40% predicted and diffusion capacity of the lung for carbon monoxide (DLco) 30%–89% predicted. Subjects taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months were allowed to participate. Subjects were randomised to receive nintedanib or placebo stratified by anti-topoisomerase I antibody (ATA) status. Subjects received trial medication until the last subject had reached week 52 but for ≤100 weeks.

The primary endpoint in the SENSCIS trial was the rate of decline in FVC (mL/year) assessed over 52 weeks. In these post-hoc analyses, we analysed the rate of decline in FVC (mL/year) over 52 weeks in subjects with early SSc (<18 months since first non-Raynaud symptom), elevated inflammatory markers (C reactive protein ≥6 mg/L and/or platelets ≥$330\times10^9$/L) or significant skin fibrosis (assessed using two approaches: modified Rodnan skin score (mRSS) 15–40 or mRSS ≥18) at baseline. We also analysed this endpoint in subjects with one of these factors plus dcSSc. The statistical models were fitted analogously to the prespecified subgroup analyses of the endpoint.[16] The rate of decline in FVC was based on a linear mixed-effects model for longitudinal data (with random intercepts and slopes on the patient level). It was based on all measurements taken over 52 weeks, including those from subjects who discontinued trial medication. Absolute changes from baseline in DLco % predicted at week 52 were analysed using a mixed model for repeated measures. Further, we descriptively assessed the prevalence of combinations of risk factors (intersecting sets) in the study sample.

## RESULTS

The rate of decline in FVC was analysed in 575 subjects (287 treated with nintedanib, 288 with placebo). Of these subjects, 79 (13.7%) had <18 months since first non-Raynaud symptom, 210 (36.5%) had elevated inflammatory markers, 172 (29.9%) had mRSS 15–40 and 129 (22.4%) had mRSS ≥18. The baseline characteristics of these subgroups are shown in table 1. Of 299 subjects with dcSSc, 29 (9.7%) had <18 months since first non-Raynaud symptom, 129 (43.1%) had elevated inflammatory markers, 162 (54.2%) had mRSS 15–40 and 129 (43.1%) had mRSS ≥18.

In the placebo group, the rate of decline in FVC over 52 weeks was −93.3 mL/year. Compared with all subjects in the placebo group, the rate of decline in FVC was numerically greater in subjects with <18 months since first non-Raynaud symptom (−167.8 mL/year), with elevated inflammatory markers (−100.7 mL/year), with mRSS 15–40 (−121.7 mL/year) and with mRSS ≥18 (−131.7 mL/year) (figure 1A). The rate of decline in FVC was also numerically greater in subjects with one of these factors plus dcSSc than in all subjects in the placebo group (figure 1B). The rate of decline in FVC was numerically lower in subjects treated with nintedanib than placebo across the subgroups in the overall population (figure 1A) and in subjects with dcSSc (figure 1B).

Analysis of intersecting sets of risk factors showed that combinations with dcSSc were frequent, while other (bivariate) combinations were less prevalent (online supplemental figure 1). The distribution of risk factor combinations was similar in both treatment groups (online supplemental table 1).

## DISCUSSION

The SENSCIS trial included a broad population of subjects with fibrosing SSc-ILD, including those with early SSc, elevated inflammatory markers and extensive skin fibrosis, which are considered risk factors for the progression of SSc-ILD. Our analyses of data from the placebo group show that these factors, particularly early SSc (<18 months since first non-Raynaud symptom), were associated with a greater rate of decline in FVC over 52 weeks. The effect of nintedanib on reducing the rate of decline in FVC was numerically greater in patients with risk factors for rapid SSc-ILD progression than in the overall trial population.

Patients with early dcSSc and elevated acute phase reactants appear to benefit from treatment with the interleukin-6 inhibitor tocilizumab.[17] The current analyses suggest that patients with early SSc who have lung fibrosis may also benefit from nintedanib. Inflammation and fibrosis are early events in the pathogenesis of SSc-ILD and often coexist. Nintedanib inhibits key fibrotic and inflammatory pathways leading to pulmonary fibrosis, including the release of pro-fibrotic mediators, the proliferation and migration of fibroblasts, and the deposition of extracellular matrix.[15] Our data suggest that nintedanib slows the progression of pulmonary fibrosis in patients with SSc-ILD irrespective of risk factors for progression. These findings are supported by previous analyses

**Table 1** Baseline characteristics in subjects with risk factors for rapid decline in FVC in the SENSCIS trial

| | <18 months since onset of first non-Raynaud symptom | | Elevated inflammatory markers* | | mRSS 15–40 | | mRSS ≥18 | |
|---|---|---|---|---|---|---|---|---|
| | Nintedanib (n=40) | Placebo (n=39) | Nintedanib (n=104) | Placebo (n=106) | Nintedanib (n=96) | Placebo (n=76) | Nintedanib (n=69) | Placebo (n=60) |
| Age (years) | 56.3 (11.3) | 52.6 (14.5) | 53.0 (12.6) | 53.6 (12.5) | 52.5 (12.1) | 49.5 (13.5) | 52.2 (12.3) | 48.6 (13.7) |
| Female | 29 (72.5) | 25 (64.1) | 81 (77.9) | 75 (70.8) | 72 (75.0) | 61 (80.3) | 52 (75.4) | 49 (81.7) |
| Years since onset of first non-Raynaud symptom | 1.0 (0.4) | 0.9 (0.4) | 3.3 (1.5) | 3.4 (1.7) | 3.7 (1.7) | 4.1 (1.9) | 3.8 (1.7) | 4.0 (1.8) |
| Diffuse cutaneous SSc | 16 (40.0) | 13 (33.3) | 65 (62.5) | 64 (60.4) | 91 (94.8) | 71 (93.4) | 69 (100.0) | 60 (100.0) |
| ANA positive | 31 (77.5) | 31 (79.5) | 83 (79.8) | 83 (78.3) | 72 (75.0) | 62 (81.6) | 53 (76.8) | 49 (81.7) |
| ATA positive | 19 (47.5) | 22 (56.4) | 69 (66.3) | 64 (60.4) | 68 (70.8) | 48 (63.2) | 51 (73.9) | 36 (60.0) |
| ARA positive | 3 (7.5) | 5 (12.8) | 7 (6.7) | 9 (8.5) | 7 (7.3) | 8 (10.5) | 7 (10.1) | 8 (13.3) |
| ACA positive | 4 (10.0) | 7 (17.9) | 6 (5.8) | 10 (9.4) | 4 (4.2) | 4 (5.3) | 3 (4.3) | 4 (6.7) |
| Extent of fibrotic ILD on HRCT (%)† | 33.9 (20.8) | 33.1 (20.3) | 36.4 (21.9) | 37.0 (21.6) | 37.5 (23.1) | 39.3 (20.9) | 36.4 (22.1) | 41.3 (22.5) |
| Presence of honeycombing on HRCT | 4 (10.0) | 11 (28.2) | 17 (16.3) | 22 (20.8) | 13 (13.5) | 10 (13.2) | 9 (13.0) | 5 (8.3) |
| Presence of reticulation on HRCT | 33 (82.5) | 38 (97.4) | 95 (91.3) | 98 (92.5) | 88 (91.7) | 70 (92.1) | 64 (92.8) | 52 (86.7) |
| Presence of ground-glass opacities on HRCT | 32 (80.0) | 38 (97.4) | 89 (85.6) | 92 (86.8) | 85 (88.5) | 62 (81.6) | 60 (87.0) | 50 (83.3) |
| FVC (mL) | 2601 (925) | 2595 (942) | 2405 (757) | 2483 (878) | 2410 (713) | 2402 (817) | 2354 (697) | 2419 (865) |
| FVC % predicted | 75.1 (17.8) | 71.6 (16.5) | 70.0 (15.2) | 70.4 (16.0) | 68.7 (16.9) | 69.6 (16.2) | 67.4 (14.3) | 69.3 (16.1) |
| DLco % predicted‡ | 57.0 (15.7) | 54.9 (15.7) | 49.8 (14.5) | 49.3 (14.5) | 51.7 (17.3) | 53.8 (15.1) | 51.5 (16.6) | 51.6 (14.7) |
| $SpO_2$ (%) | 97.4 (1.9) | 97.0 (3.9) | 97.3 (2.0) | 97.3 (2.5) | 97.3 (2.1) | 97.2 (3.3) | 97.2 (2.2) | 97.0 (3.1) |
| mRSS | 10.6 (10.4) | 10.4 (9.2) | 12.9 (9.8) | 12.7 (9.6) | 21.7 (5.9) | 21.1 (4.8) | 24.5 (6.2) | 24.7 (6.6) |
| Immunosuppressants§ | 34 (85.0) | 27 (69.2) | 96 (92.3) | 96 (90.6) | 91 (94.8) | 65 (85.5) | 67 (97.1) | 52 (86.7) |
| Most commonly used immunosuppressants¶ | | | | | | | | |
| Mycophenolate mofetil | 14 (35.0) | 7 (17.9) | 50 (48.1) | 58 (54.7) | 50 (52.1) | 39 (51.3) | 40 (58.0) | 31 (51.7) |
| Acetylsalicylic acid | 7 (17.5) | 6 (15.4) | 19 (18.3) | 31 (29.2) | 17 (17.7) | 22 (28.9) | 13 (18.8) | 16 (26.7) |
| Prednisone | 7 (17.5) | 3 (7.7) | 24 (23.1) | 17 (16.0) | 23 (24.0) | 9 (11.8) | 19 (27.5) | 9 (15.0) |
| Prednisolone | 6 (15.0) | 8 (20.5) | 15 (14.4) | 19 (17.9) | 14 (14.6) | 9 (11.8) | 11 (15.9) | 7 (11.7) |
| Methotrexate | 4 (10.0) | 2 (5.1) | 7 (6.7) | 5 (4.7) | 11 (11.5) | 2 (2.6) | 8 (11.6) | 3 (5.0) |
| Corticosteroids§ | 21 (52.5) | 17 (43.6) | 61 (58.7) | 59 (55.7) | 58 (60.4) | 28 (36.8) | 43 (62.3) | 25 (41.7) |

Data are n (%) or mean (SD). Not all subjects provided data for all variables.
*C reactive protein ≥6 mg/L and/or platelets ≥$330\times10^9$/L.
†Assessed in whole lung to nearest 5% by central review. Pure (non-fibrotic) ground-glass opacity was not included.
‡Corrected for haemoglobin.
§Customised drug grouping.
¶Taken by >10% of patients in the nintedanib and/or placebo group in any subgroup.
ACA, anti-centromere antibody; ANA, anti-nuclear antibody; ARA, anti-RNA polymerase III antibody; ATA, anti-topoisomerase I antibody; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; $SpO_2$, oxygen saturation; SSc, systemic sclerosis.

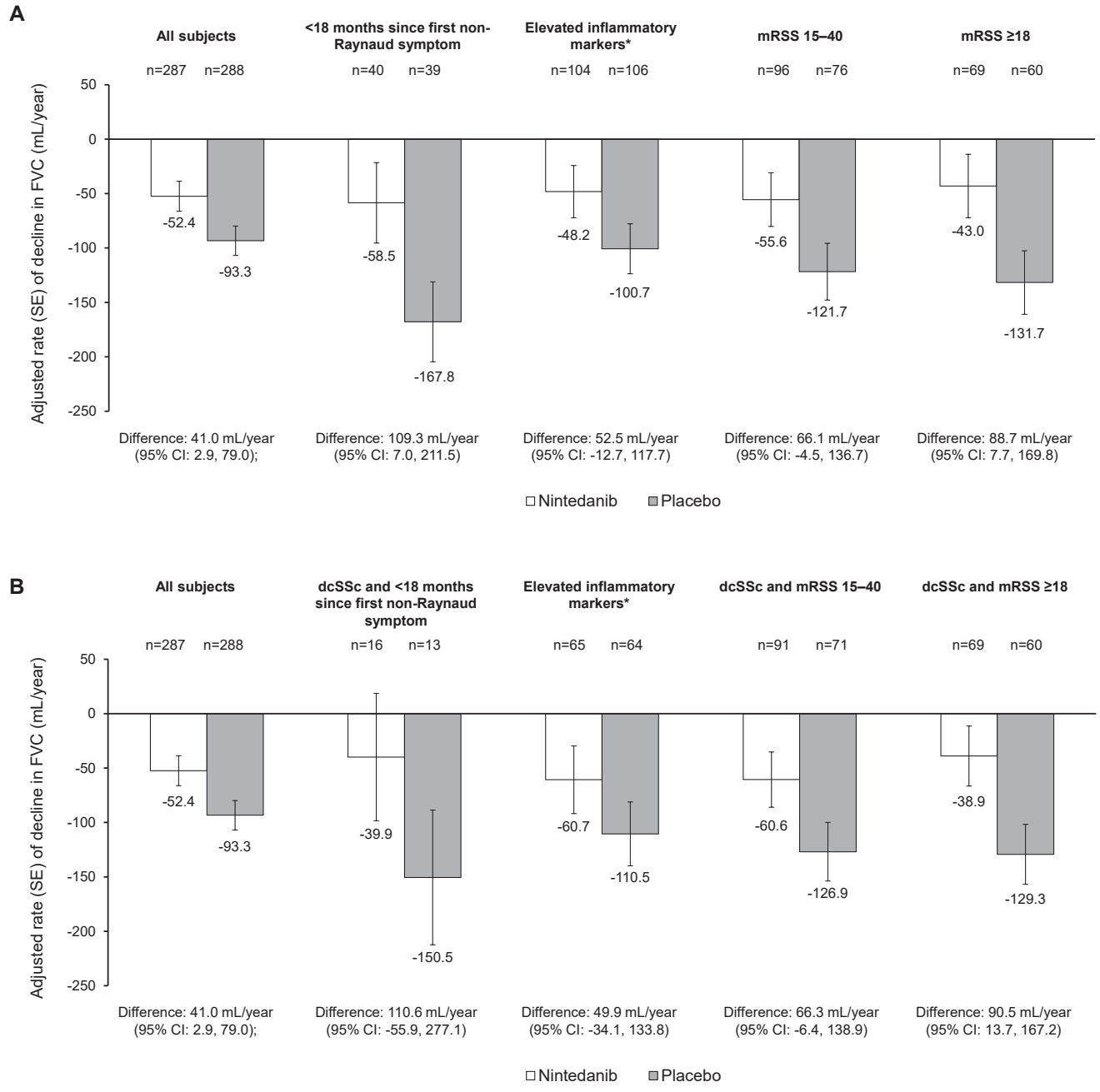


**Figure 1** Rate of decline in FVC (mL/year) over 52 weeks (A) in all subjects and in subjects with risk factors for rapid decline in FVC at baseline and (B) in all subjects and in subjects with dcSSc and risk factors for rapid decline in FVC at baseline in the SENSCIS trial. *C reactive protein ≥6 mg/L and/or platelets ≥330×$10^9$/L. dcSSc, diffuse cutaneous systemic sclerosis; FVC, forced vital capacity; mRSS, modified Rodnan skin score.

showing that nintedanib slows FVC decline in subjects with SSc-ILD across subgroups based on ATA status, the severity of lung function impairment or the presence of respiratory symptoms at baseline.[18 19] Previous analyses of data from the SENSCIS trial have shown that nintedanib reduced the rate of decline in FVC both in subjects who were and were not taking mycophenolate at baseline,[20] suggesting that targeting fibrosis with nintedanib slows the progression of SSc-ILD even in patients receiving immunomodulatory therapy to address the inflammatory component of the disease. More data are needed on the risk:benefit of earlier combination therapy for SSc-ILD versus sequential therapy, but these results suggest that there may be a benefit of introducing nintedanib early in the course of fibrosing SSc-ILD.

Strengths of these analyses include the standardised collection of FVC data over 52 weeks in the setting of a randomised controlled trial. Limitations include that the SENSCIS trial was not designed to assess the impact of risk factors on decline in FVC and patients were not randomised by these factors; thus, there were differences in the characteristics of the subgroups at baseline and the derived estimates are subject to substantial uncertainty. In particular, there was an unequal distribution of mycophenolate use across the subgroups based on risk factors. This hampered the comparability of FVC decline, and consequently estimates of treatment effects, across the subgroups based on risk factors. Interpretation of groups of small size should be approached with caution. This analysis was driven by hypotheses about risk factors for rapid progression and did not involve screening of an array of patient-level variables that might be influential. Assessing interaction effects between the explored risk factors would be of interest; however, apart from bivariate interactions with the diffuse cutaneous subtype of SSc, robust modelling of longitudinal data was precluded by sample size limitations.

In conclusion, subjects with SSc-ILD in the SENSCIS trial who had early SSc, elevated inflammatory markers or extensive skin fibrosis had a more rapid decline in FVC over 52 weeks than the overall trial population. Nintedanib reduced the rate of decline in FVC across the subgroups based on risk factors for rapid FVC decline. These results support the prompt initiation of nintedanib in patients with fibrosing SSc-ILD to preserve lung function and improve patient outcomes.

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To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use https://vivli.org/ to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.



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