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 ≥330x10^9/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.

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. A decline in forced vital capacity (FVC) in patients with SSc-ILD is associated with an increased risk of mortality. Although the course of SSc-ILD is variable, risk factors for decline in FVC have been identified. These include short SSc duration, male sex, elevated inflammatory markers and progression of skin fibrosis. Diffuse cutaneous SSc (dcSSc) has been identified as a risk factor for decline in FVC in some but not all studies.

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. 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.

Nintedanib is an intracellular inhibitor of tyrosine kinases that has anti-fibrotic and anti-inflammatory effects that inhibit pathways involved in fibrosis. 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%. 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. 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 ≥6 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 ≥330×10⁹/L) or significant skin fibrosis (assessed using two approaches: modified Rodnan skin score (mRSS) 15–40 or mRSS ≥18) 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).

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. 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 profibrotic mediators, the proliferation and migration of fibroblasts, and the deposition of extracellular matrix. 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 showing that nintedanib slows FVC decline in...
## Table 1  Baseline characteristics in subjects with risk factors for rapid decline in FVC in the SENSCIS trial

| Age (years) | Female | Years since onset of first non-Raynaud symptom | Diffuse cutaneous SSc | ANA positive | ATA positive | ARA positive | ACA positive | Extent of fibrotic ILD on HRCT (%)† | Presence of honeycombing on HRCT | Presence of reticulation on HRCT | Presence of ground-glass opacities on HRCT | SpO2 (%) | FVC (mL) | FVC % predicted | DLco % predicted‡ | Immunosuppressants§ | Most commonly used immunosuppressants¶ | Corticosteroids§ |
| Nintedanib (n=40) | 56.3 (11.3) | 29 (72.5) | 1.0 (0.4) | 16 (40.0) | 31 (77.5) | 19 (47.5) | 3 (7.5) | 4 (10.0) | 33 (82.5) | 32 (80.0) | 2601 (925) | 75.1 (17.8) | 57.0 (15.7) | 97.4 (1.9) | 10.6 (10.4) | 34 (85.0) | 14 (35.0) | 7 (17.9) |
| Placebo (n=39) | 52.6 (14.5) | 25 (64.1) | 0.9 (4.1) | 13 (33.3) | 31 (79.5) | 22 (56.4) | 12 (28.2) | 7 (17.9) | 38 (97.4) | 38 (97.4) | 2595 (942) | 71.6 (16.5) | 54.9 (15.7) | 97.0 (3.9) | 10.4 (9.2) | 27 (69.2) | 7 (17.9) | 50 (48.1) |
| Nintedanib (n=104) | 53.0 (12.6) | 81 (77.9) | 3.3 (1.5) | 65 (23.5) | 83 (79.8) | 69 (66.3) | 7 (6.7) | 6 (5.8) | 95 (91.3) | 89 (85.6) | 2405 (757) | 70.4 (15.2) | 49.8 (14.5) | 97.3 (2.0) | 12 (9.8) | 96 (92.3) | 7 (17.9) | 50 (48.1) | 58 (54.7) |
| Placebo (n=106) | 53.6 (12.5) | 75 (70.8) | 3.4 (1.7) | 64 (60.4) | 83 (78.3) | 64 (60.4) | 9 (8.5) | 10 (9.4) | 98 (92.5) | 92 (86.8) | 2483 (878) | 70.4 (15.2) | 49.3 (14.5) | 97.3 (2.5) | 12 (9.8) | 96 (90.6) | 7 (17.9) | 50 (48.1) | 58 (54.7) |
| Nintedanib (n=96) | 52.5 (12.1) | 72 (75.0) | 3.7 (1.7) | 91 (94.8) | 72 (75.0) | 68 (70.8) | 7 (7.3) | 4 (4.2) | 88 (91.7) | 85 (88.5) | 2410 (713) | 68.7 (16.9) | 51.7 (17.3) | 97.3 (2.1) | 21.7 (5.9) | 91 (94.8) | 7 (17.9) | 50 (48.1) | 58 (54.7) |
| Placebo (n=76) | 49.5 (13.5) | 61 (80.3) | 4.1 (1.9) | 71 (93.4) | 62 (81.6) | 48 (63.2) | 8 (10.5) | 4 (5.3) | 70 (92.1) | 62 (81.6) | 2402 (817) | 69.6 (16.2) | 53.8 (15.1) | 97.2 (3.3) | 21.1 (4.8) | 65 (85.5) | 7 (17.9) | 50 (48.1) | 58 (54.7) |
| Nintedanib (n=69) | 52.2 (12.3) | 52 (75.4) | 3.8 (1.7) | 69 (100.0) | 53 (76.8) | 51 (73.9) | 7 (10.1) | 3 (4.3) | 64 (92.8) | 60 (87.0) | 2354 (697) | 67.4 (14.3) | 51.5 (16.6) | 97.2 (2.2) | 24.5 (6.2) | 67 (97.1) | 7 (17.9) | 50 (48.1) | 58 (54.7) |
| Placebo (n=60) | 48.8 (13.7) | 49 (81.7) | 4.0 (1.8) | 60 (100.0) | 49 (81.7) | 36 (60.0) | 8 (13.3) | 4 (6.7) | 52 (86.7) | 50 (83.3) | 2419 (865) | 69.3 (16.1) | 51.6 (14.7) | 97.0 (3.1) | 24.7 (6.6) | 52 (86.7) | 7 (17.9) | 50 (48.1) | 58 (54.7) |

Data are n (%) or mean (SD). Not all subjects provided data for all variables.

* C reactive protein ≥6 mg/L and/or platelets ≥330×10⁹/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-SSA/Ro antigen; 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; SpO₂, oxygen saturation; SSc, systemic sclerosis.


subjects with SSc-ILD across subgroups based on ATA status, the severity of lung function impairment or the presence of respiratory symptoms at baseline.\textsuperscript{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,\textsuperscript{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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Acknowledgements
We thank the patients who participated in the SENSCIS trial. The authors did not receive payment for development of this manuscript. Elizabeth Ng and Wendy Morris of Fleishman Hillard, London, UK, provided writing assistance, which was contracted and funded by Boehringer Ingelheim (BI). BI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Contributors
DK, TMM, YA, VS, SA, MKreuter, A-MH-V, Mkuwana and CPD were involved in the acquisition of data. CS was involved in data analysis. All authors were involved in the interpretation of the data and in drafting the article or revising it for critically important content. All authors approved the final version of the manuscript.

Funding
The SENSCIS trial was funded by Boehringer Ingelheim International GmbH.

Competing interests
DK reports grants from Bristol Myers Squibb, Horizon Therapeutics and Pfizer; consulting fees from AbbVie, BI, Bristol Myers Squibb, CSL Behring, Genentech, Horizon Therapeutics, Janssen, Prometheus, Talaris and Theravy; fees for presentations from AbbVie, BL, CSL Behring, Genentech, Horizon Therapeutics and Janssen; has a leadership or fiduciary role with Eicos; has received royalties or licences for the University of California Los Angeles Scleroderma Clinical Trials Consortium (SCTC) Gastrointestinal Tract instrument 2.0; and owns stock in Eicos. TMM reports consulting fees from AstraZeneca, Bayer, Blade Therapeutics, BI, Bristol Myers Squibb, Galapagos, Galexto, GlaxoSmithKline, IQVIA, Pliant, Respivant Sciences, Roche/GeneTech, Theravance Biopharma and Veracyte; and fees for presentations from BL and Roche/GeneTech. ERV reports grants from BL, Forbiius, Kadmon and Horizon; and fees from BI for serving on advisory boards and for presentations. YA reports consulting fees from BI and Sanofi; fees for presentations from AbbVie, BI and Janssen; and has participated on Data Safety Monitoring Boards or advisory boards for BI, Chemomab, Curzon, Medisenic, Menarini, Prometheus and Sanofi. VS reports grants paid to her institution from the Belgian Fund for Scientific Research in Rheumatic Diseases, Research Foundation Flanders, BI and Janssen-Cilag; consulting fees and fees for presentations paid to herself and to her institution from BI; consulting fees paid to her institution from Janssen-Cilag; fees for presentations paid to her institution from Janssen-Cilag and UCS; support for travel paid to her institution by BI; and holds unpaid roles with the ACR and EULAR study groups on microcirculation, ERN-ReConNET and the SCTC working group on capillaroscopy. SA reports grants paid to his institution from BL, Janssen and Merck; consulting fees from AbbVie, AstraZeneca, BL, Corbus, CSL Behring and Novartis; and fees for presentations from Integrity Continuing Education. Mkuwana reports consulting, grants, fees and fees for presentations from BL and Roche; and holds leadership or fiduciary roles with Deutsches gesellschaft fur Pneumologie, the European Respiratory Society and the German Respiratory Society; A-MH-V reports grants from BI; consulting fees from Anx Therapeutics, Bayer, BI, Janssen, Lilly, Medscape, Merck Sharp & Dohme and Roche; fees for presentations from Anx Therapeutics, Bayer, BI, Janssen, Lilly, Medscape, Merck Sharp & Dohme and Roche; and holds leadership or fiduciary roles with EUSTAR, the Nordic PH vision group and the Norwegian SSC study group. Mkuwana reports grants paid to his institution from BL, MBL and Ono Pharmaceutical; consulting fees from BI, Chugai, Corbus and Mochida; fees for presentations from AbbVie, Asahi Kasei, Astellas, Bayer, BL, Chugai, Eisai, Janssen, Mitsubishi Tanabe and Ono Pharmaceutical; and has received royalties or licences from MBL, CS, MA and SS are employees of BI. CPD reports grants from Anx Therapeutics, CSL Behring, GlaxoSmithKline, Inventiva and Servier; consulting fees from AbbVie, Acceleron, Bayer, BI, Corbus, CSL Behring, GlaxoSmithKline, Horizon Therapeutics, Inventiva, Roche and Sanofi; and fees for presentations from BI, Corbus and Janssen.

Patient consent for publication
Not required.

Ethics approval
The SENSCIS trial was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation. The trial was approved by an independent ethics committee or institutional review board at every site. The participating sites are listed in Distler et al. All patients provided written informed consent before trial entry.

Provenance and peer review
Not commissioned; externally peer reviewed.

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