Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: subgroup analysis of the SENSCIS trial

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Summary

Background In the SENSCIS trial in patients with systemic sclerosis-associated ILD (SSc-ILD), nintedanib reduced the rate of decline in forced vital capacity (FVC). Patients on stable therapy with mycophenolate for ≥6 months before randomisation could participate. We analysed the efficacy and safety of nintedanib in subgroups by mycophenolate use at baseline.

Methods Patients with SSc-ILD were randomised to receive nintedanib or placebo for ≥52 weeks. We analysed declines in FVC over 52 weeks in pre-specified subgroups by mycophenolate use at baseline.

Findings Of 288 patients per group, 139 (48.3%) in the nintedanib group and 140 (48.6%) in the placebo group were taking mycophenolate at baseline. In patients taking mycophenolate at baseline, the mean (SE) annual rate of FVC decline was -40.2 (19.8) mL/year with nintedanib and -66.5 (19.3) mL/year with placebo (difference: 26.3 mL/year [95% CI -27.9, 80.6]). In patients not taking mycophenolate at baseline, the mean (SE) annual rate of FVC decline was -63.9 (19.3) mL/year with nintedanib and -119.3 (19.0) mL/year with placebo (difference: 55.4 mL/year [95% CI 2.3, 108.5]). Statistical testing did not indicate heterogeneity in the effect of nintedanib vs placebo on the annual rate of FVC decline between the subgroups by mycophenolate use (p=0.45 for interaction). The proportion of patients with an absolute decrease in FVC of ≥3.3% predicted was lower with nintedanib than placebo both in patients taking mycophenolate (29.0% versus 40.0%; OR: 0.61 [95% CI 0.37,1.01]) and not taking mycophenolate (39.6% versus 47.3%; OR 0.73 [95% CI 0.46, 1.16]) at baseline. The adverse event profile of nintedanib was similar between the subgroups.

Interpretation In patients with SSc-ILD, nintedanib reduced the progression of ILD, both in patients who were and were not using mycophenolate at baseline, with no heterogeneity detected between the subgroups and an adverse event profile that was manageable for most patients.

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Introduction

Systemic sclerosis (SSc) is an autoimmune disease with heterogeneous organ manifestations.[1] Interstitial lung disease (ILD) is a common manifestation of SSc and the leading cause of death in patients with SSc.[2,3] A decline in forced vital capacity (FVC) is a predictor of mortality in patients with SSc-ILD.[4,5] The mainstay of treatment for SSc is immunosuppression. Based on the results of retrospective cohort studies[6] and Scleroderma Lung Study II (SLS II),[7] which showed that treatment with oral mycophenolate for 2 years was associated with similar changes in FVC, with better tolerability, compared with oral cyclophosphamide for 1 year followed by placebo for 1 year, mycophenolate has become the preferred treatment for SSc-ILD in most countries.[8,9] However, only a single small (n=42) placebo-controlled trial of mycophenolate in patients with SSc-ILD has been conducted.

Nintedanib is an intracellular inhibitor of tyrosine kinases that has shown anti-fibrotic, anti-inflammatory and vascular remodelling effects in pre-clinical models of SSc and ILD.[10–13] Nintedanib is an approved treatment for idiopathic pulmonary fibrosis and SSc-ILD. In the phase III SENSCIS trial in patients with SSc-ILD, nintedanib 150 mg bid reduced the progression of ILD, as demonstrated by a reduction in the rate of decline in FVC over 52 weeks, with an adverse event profile that was manageable for most patients and similar to that observed in patients with IPF, but with no significant benefit on skin fibrosis assessed using the modified Rodnan skin score (mRSS) or health-related quality of life (HRQL) measured using the St. George's Respiratory Questionnaire (SGRQ).[14,15] Approximately half of the patients in the SENSCIS trial were taking a stable dose of mycophenolate at baseline. We analysed the efficacy and safety of nintedanib in subgroups of patients by the use of mycophenolate at baseline.

Methods

Study design and participants

The SENSCIS trial was a randomised, double-blind, placebo-controlled, parallel group trial conducted in 32 countries.[14] The 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 from the International Conference on Harmonisation, and was approved by local authorities. All patients provided written informed consent.

Eligibility criteria for the SENSCIS trial have been published.[14,16] Briefly, patients had to be aged ≥18 years and have SSc according to American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria[1] with onset of first non-Raynaud symptom <7 years before screening. ILD was identified based on a high-resolution computed tomography (HRCT) scan performed ≤12 months before screening (see appendix for details). Patients needed to have fibrotic ILD of ≥10% extent, confirmed by central assessment (appendix). Patients had an FVC of ≥40% of the predicted value and a diffusion capacity of the lung for carbon monoxide (DLco) (corrected for haemoglobin) of 30–89% of the predicted value.

Patients taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomisation could participate. Patients were not eligible to participate if they had received prednisone >10 mg/day (or equivalent) ≤2 weeks prior to randomisation; azathioprine, hydroxychloroquine, colchicine, D-penicillamine, or sulfasalazine ≤8 weeks prior to randomisation; or cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, cyclosporine A, newer anti-arthritic treatments such as tofacitinib , or potassium para-aminobenzoate ≤6 months prior to randomisation.

Randomisation and masking

After a screening period of ≤12 weeks, patients were randomly assigned 1:1 to receive oral nintedanib 150 mg twice daily or placebo. Randomised patients were stratified by the presence of anti-topoisomerase I antibody (ATA). The study sponsor allocated subjects via an interactive web-based response system, using a pseudo-random number generator, in block sizes of 4. Nintedanib (Boehringer Ingelheim, Biberach, Germany) and placebo were provided by the sponsor as soft gelatine capsules with identical appearance. Patients, investigators, and other personnel involved in the trial conduct and analysis were masked to treatment assignment until after database lock. The success of masking was not evaluated.

Procedures

Patients remained on blinded treatment until the last patient had reached week 52 but no longer than 100 weeks. Treatment interruptions (for ≤4 weeks for adverse events considered related to trial medication or ≤8 weeks for other adverse events) and dose reductions to 100 mg twice daily were recommended to manage adverse events. After resolution of the adverse event, nintedanib could be reintroduced or the dose increased to 150 mg twice daily. Patients who discontinued trial medication were asked to attend all scheduled visits and undergo examinations as originally planned.

For patients who entered the trial on stable therapy with mycophenolate or methotrexate, the pre-trial dose was to be continued for ≥6 months after randomisation. For any patient, initiation of immunosuppressive therapy restricted at randomisation was allowed during the trial in cases of clinically significant deterioration, as previously described.[14]

Outcomes

The primary endpoint was the annual rate of decline in FVC (mL/year) assessed over 52 weeks. Key secondary endpoints were absolute changes from baseline in mRSS and SGRQ total score at week 52. The mRSS evaluates a patient's skin thickness through palpation of 17 areas using

a scale of 0 to 3 to give a maximum score of 51, with higher scores indicating worse skin fibrosis.[17] The SGRQ is a self-administered 50-item questionnaire, comprising three domains (symptoms, activity, impact), which assesses HRQL in patients with respiratory disease.[18] Domain and total scores range from 0 to 100, with higher scores indicating worse HRQL. Other endpoints included the annual rate of decline in FVC % predicted, the absolute change from baseline in FVC (mL) at week 52, the percentages of patients who had absolute declines from baseline in FVC of >5% predicted and >10% predicted at week 52, and the percentages of patients who had relative declines from baseline in FVC (mL) of >5% and >10% at week 52. We also assessed post-hoc the percentages of patients who had an absolute increase in FVC of ≥3.0% predicted, stable FVC (absolute increase <3.0% predicted or decrease <3.3% predicted) and an absolute decrease in FVC of ≥3.3% predicted at week 52; these correspond to the proposed minimal clinically important difference (MCID) estimates for improvement in FVC, stable FVC, and worsening of FVC based on analyses of data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36 (SF-36).[19] The proportion of patients who died was analysed over the entire trial period. Safety was assessed based on adverse events reported, irrespective of causality, over 52 weeks (or until 28 days after last trial drug intake for patients who discontinued trial drug before week 52). Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities, version 21.1.

Statistical analysis

The analyses conducted in all patients have been described.[14] Here we report the results of analyses in subgroups of patients by use of mycophenolate (mofetil or sodium) at baseline. All analyses were conducted in patients who received ≥1 dose of trial medication. The annual rate of decline in FVC (mL/year) was analysed in the subgroups using a random coefficient regression model (with random slopes and intercepts) including ATA status (ATA positive, ATA

negative), age, height, sex and baseline FVC (mL) as covariates and interaction terms for baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time. The analysis was based on all measurements taken within the first 52 weeks, including those from patients who discontinued study drug. The model allowed for missing data, assuming they were missing at random. Changes from baseline in mRSS and SGRQ total score at week 52 were analysed in the subgroups using a restricted maximum likelihood (REML) based repeated measures approach. The analyses included fixed categorical effects of ATA status (positive, negative), visit, and treatment−by−subgroup−by−visit interaction and fixed continuous effect of baseline−by−visit. A least-squares mean estimate statement, with appropriate contrasts, was used to conduct an F-test of heterogeneity between the subgroups. Thus, the interaction p-value was an indicator of the potential heterogeneity in the treatment effect of nintedanib versus placebo between the subgroups by mycophenolate use. In the analysis of categorical changes in FVC (% predicted or mL) at week 52, data from patients with missing values at week 52 were imputed using a worst value carried forward approach; it seemed reasonable to assume that missing FVC data at week 52 were missing at random as the majority of patients (42 of 78) who had missing FVC data at week 52 had non-missing FVC data until week 36 or after week 52. Statistical analyses of other endpoints are described in the appendix. Adverse events reported in subgroups by mycophenolate use at baseline are presented descriptively. Analyses of the primary endpoint, key secondary endpoints and adverse events in subgroups by mycophenolate use, including the corresponding tests for treatment-by-subgroup interaction,were pre-specified. The other analyses described in this paper were post-hoc.

Role of the funding source

The sponsor participated in the study design, data collection, statistical analyses, data interpretation, and the writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were recruited between November 2015 and October 2017. A total of 576 patients received ≥1 dose of nintedanib or placebo (288 in each group). At baseline, 139 patients (48.3%) in the nintedanib group and 140 patients (48.6%) in the placebo group were taking mycophenolate (appendix). Compared with patients not taking mycophenolate, a greater proportion had diffuse cutaneous SSc (54.8% versus 49.2%), mean mRSS was higher (11.9 [SD 8.9]) versus 10.4 [SD 9.0] and mean FVC % predicted was lower (70.8 [SD 16.0] versus 74.2 [SD 17.1] % predicted) (Table 1). Of the patients who were taking mycophenolate at baseline, 267 of 279 (95.7%) were still taking mycophenolate at week 52. Only 11 of 297 (3.7%) patients (5 in the nintedanib group, 6 in the placebo group) who were not taking mycophenolate at baseline started mycophenolate during the 52 weeks of trial treatment.

Patient disposition is shown in Figure 1. Smaller proportions of nintedanib-treated patients in both subgroups by mycophenolate use completed 52 weeks treatment (82.7% of those taking mycophenolate, 78.5% of those not taking mycophenolate) compared with placebo-treated patients (92.9% and 85.8%, respectively). Mean exposure to trial medication over 52 weeks was slightly lower in nintedanib-treated patients who were and were not taking mycophenolate at baseline (10.7±3.3 months and 10.3±3.6 months, respectively) compared with placebo-treated patients (11.6±2.0 and 11.1±2.7 months, respectively).

Nintedanib was associated with a reduced rate of FVC decline both in patients who were and were not taking mycophenolate at baseline (Figure 2A, Table 2). In both subgroups by mycophenolate use, the curves of change from baseline in FVC in the nintedanib and placebo groups started to separate by week 12 and continued to diverge until week 52 (Figure 2B). In the placebo group, the mean (SE) rate of decline in FVC over 52 weeks was -66.5 (19.3)

mL/year in patients taking mycophenolate at baseline and -119.3 (19.0) mL/year in patients not taking mycophenolate at baseline. The treatment effect of nintedanib on the rate of FVC decline was numerically greater in patients who were not taking mycophenolate at baseline (difference: 55.4 mL/year [95% CI 2.3, 108.5]) than in those who were (difference: 26.3 mL/year [95% CI -27.9, 80.6]), corresponding to relative reductions of 46% and 40%, respectively. Statistical testing did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups by mycophenolate use (p=0.45 for treatment-by-time-by-subgroup interaction). The treatment effect in both subgroups was in the range of the treatment effect in the overall population (41.0 mL/year [95% CI 2.9, 79.0]; p=0.04).

The proportion of patients with an absolute increase in FVC of ≥3.0% predicted at week 52 was similar between nintedanib and placebo in patients taking mycophenolate at baseline (21.0% and 20.7%, respectively; OR: 1.01 [95% CI 0.57,1.81]) but greater with nintedanib than placebo in those not taking mycophenolate at baseline (24.8% versus 9.5%; OR: 3.17 [95% CI 1.63, 6.16]) (Figure 2C). The proportion of patients with stable FVC (absolute increase <3.0% predicted or decrease <3.3% predicted) was greater in the nintedanib group than in the placebo group in patients taking mycophenolate at baseline (50.0% versus 39.3%; OR: 1.54 [95% CI 0.96, 2.49]), but lower with nintedanib than placebo in patients not taking mycophenolate at baseline (35.6% versus 43.2%; OR: 0.72 [95% CI 0.45,1.16]) (Figure 2C). The proportion of patients with an absolute decrease in FVC of ≥3.3% predicted was lower with nintedanib than placebo in patients taking mycophenolate at baseline (29.0% versus 40.0%; OR: 0.61 [95% CI 0.37,1.01]) and not taking mycophenolate at baseline (39.6% versus 47.3%; OR 0.73 [95% CI 0.46, 1.16]) (Figure 2C).

In the nintedanib and placebo groups, respectively, absolute declines in FVC >5% predicted were seen in 15.2% and 25.7% of patients taking mycophenolate at baseline and 25.5% and 31.1% of those not taking mycophenolate at baseline, and absolute declines in FVC >10%

predicted were seen in 2.9% and 5.0% of patients taking mycophenolate at baseline and 10.7% and 11.5% of those not taking mycophenolate at baseline (Table 2). In the overall population, there was no significant difference between nintedanib and placebo in change from baseline in mRSS (difference -0.2 [95% CI -0.9, 0.5]) or SGRQ total score (difference 1.7 [95% CI -0.7, 4.1]) at week 52.[14] Statistical testing did not indicate heterogeneity in the effect of nintedanib versus placebo in change in mRSS or SGRQ total score between subgroups by use of mycophenolate at baseline (Table 2).

The adverse event profile of nintedanib was generally similar in the subgroups by mycophenolate use (Table 3). The proportions of patients with adverse events that led to discontinuation of trial medication in the nintedanib and placebo groups, respectively, were 10.8% and 6.4% in patients who were taking mycophenolate at baseline and 20.8% and 10.8% in those who were not. The most frequent adverse event reported was diarrhoea. The proportions of patients with diarrhoea adverse events in the nintedanib and placebo groups, respectively, were 76.3% and 34.3% in patients who were taking mycophenolate at baseline and 75.2% and 29.1% in those who were not. In the nintedanib group, diarrhoea led to treatment discontinuation in 7 patients (5.0%) who were taking mycophenolate at baseline and 13 patients (8.7%) who were not; in the placebo group, diarrhoea led to treatment discontinuation in one patient, who was taking mycophenolate at baseline. In the nintedanib and placebo groups, respectively, serious diarrhoea adverse events were reported for 2 patients (1.4%) and 1 patient (0.7%) who were taking mycophenolate at baseline, and no patients and 1 patient (0.7%) who were not. Of the 106 nintedanib-treated patients who were taking mycophenolate at baseline and experienced ≥1 diarrhoea AE, 73 (68.9%) experienced 1 or 2 events, 97 (91.5%) experienced events that were at worst of mild or moderate intensity, 32 (30.2%) experienced events that led to permanent dose reduction, and 7 (6.6%) experienced events that led to treatment discontinuation. Of the 112 nintedanib-treated patients who were

not taking mycophenolate at baseline and experienced ≥1 diarrhoea AE, 80 (71.4%) experienced 1 or 2 events, 109 (97.3%) experienced events that were at worst of mild or moderate intensity, 25 (22.3%) experienced events that led to permanent dose reduction, and 13 (11.6%) experienced events that led to treatment discontinuation.

The proportions of patients with abdominal pain in the nintedanib and placebo groups, respectively, were 10.1% and 4.3% in patients who were taking mycophenolate at baseline and 12.8% and 10.1% in those who were not. The proportions of patients with weight loss in the nintedanib and placebo groups, respectively, were 7.2% and 2.9% in patients who were taking mycophenolate at baseline and 16.1% and 5.4% in those who were not. The proportions of patients with upper respiratory tract infection, fatigue and headache were greater among patients who were taking mycophenolate at baseline than those who were not, but were similar between the nintedanib and placebo groups. Over the entire trial period, 19 patients died, of whom 6 (4 in the nintedanib group and 2 in the placebo group) were taking mycophenolate at baseline.

Discussion

The SENSCIS trial is the largest clinical trial to have been conducted in patients with SSc-ILD. Reflecting clinical practice in the participating countries, approximately half of the 576 patients in the trial were taking mycophenolate at baseline, making the mycophenolate users in this trial the largest cohort of patients with SSc-ILD taking mycophenolate to have been included in a clinical trial. Nintedanib reduced the progression of ILD both in patients who were and were not taking mycophenolate at baseline. While the absolute effect of nintedanib versus placebo on reducing the rate of decline in FVC was numerically lower in patients who were taking mycophenolate at baseline than in those who were not (26.3 versus 55.4 mL/year), the relative treatment effect of nintedanib was similar between these subgroups (40% and 46%, respectively) and consistent with that observed in the overall population (44%).[14]

Mycophenolate suppresses the proliferation of T- and B-lymphocytes and induces apoptosis of activated T-lymphocytes,[20] while nintedanib has demonstrated a number of anti-fibrotic, anti-inflammatory and vascular remodelling effects in pre-clinical models of SSc and SSc-ILD.[11–13] The numerical reduction in the rate of FVC decline provided by nintedanib in patients taking mycophenolate suggests that combining immunosuppression with nintedanib may provide additional benefit in reducing the progression of ILD. This is supported by the finding that among patients taking mycophenolate at baseline, a smaller proportion of patients treated with nintedanib than placebo had a decline in FVC of ≥3.3% predicted, which has been estimated as the MCID for worsening in FVC.[19] Furthermore, the annual rate of decline in FVC in patients taking mycophenolate at baseline who were treated with nintedanib (40.2 mL/year) was close to the annual rate of decline in FVC observed in healthy adults.[21]

In the placebo group, the adjusted mean rate of decline in FVC in patients who were not taking mycophenolate at baseline was -119.3 mL/year, close to the assumptions made in the calculation of the sample size for this trial. Although this large and prospectively collected dataset provides some insights into the interplay of different treatment modalities, our ability to draw conclusions on the effect of mycophenolate on lung function is limited, as patients were not randomised by use of mycophenolate. Of note, there were differences between the subgroups by mycophenolate use at baseline, including a lower FVC in the mycophenolate users. Further, it must be remembered that patients using mycophenolate were only eligible to enter the trial if they had taken a stable dose of mycophenolate for ≥6 months prior to randomisation. Thus the patients using mycophenolate at baseline were not new mycophenolate users, but rather a selected population who were tolerators of mycophenolate and potentially more likely to be responders to mycophenolate. As such, assessing the benefits of initial combination therapy versus individual components or a sequential approach to treatment was not within the scope of this trial. A further limitation of our analyses is the limited

availability of data characterising the mycophenolate users in terms of their duration of mycophenolate use prior to the trial, the dose of mycophenolate used, or their FVC trajectory prior to the trial.

Both mycophenolate[22] and nintedanib[23] are associated with gastrointestinal adverse events, while SSc itself is commonly associated with gastrointestinal problems.[24] Mycophenolate is also associated with an increased risk of infection.[22] Importantly, with the caveat that this was a population of patients who had tolerated mycophenolate for at least 6 months before entering the trial, the combination of nintedanib plus mycophenolate appeared to have acceptable tolerability. The proportion of patients with diarrhoea was similar between nintedanib-treated patients who were and were not taking mycophenolate at baseline. Upper respiratory tract infections were more common among patients taking mycophenolate but were not increased with nintedanib compared with placebo. Premature discontinuations were less common among patients taking mycophenolate but were more frequent with nintedanib than placebo in both subgroups.

In conclusion, in patients with SSc-ILD, nintedanib reduced the progression of ILD, both in patients who were and were not using mycophenolate at baseline, with no heterogeneity detected between the subgroups, and an adverse event profile that permitted most patients to remain on nintedanib throughout the trial. Given the frequent use of mycophenolate in patients with SSc-ILD, these data provide important information on the potential concomitant use of nintedanib and mycophenolate in patients with SSc-ILD.

Contributors

KBH, OD, MK, AA, MDM, GR, MGa, ECB, MGi, SS and TMM were involved in the design of the SENSCIS trial. KBH, OD, MK, YA, AB, CPD, JHWD, AMHV, DK, MDM, MV, and TMM were

investigators in the SENSCIS trial. All authors were involved in the interpretation of the data and in the writing and critical review of the manuscript.

Declaration of interests

KBH reports grants and personal fees from Actelion Pharmaceuticals, Boehringer Ingelheim and United Therapeutics; personal fees from Bayer; and grants from Genentech, Eiger BioPharmaceuticals and Reata Pharmaceuticals. OD reports grant support and lecture fees from Actelion; fees for project scoring from AbbVie and Pfizer; consulting fees from Acceleron Pharma, Anamar, Amgen, Blade Therapeutics, CSL Behring, ChemomAb, Ergonex, Glenmark Pharma, GlaxoSmithKline, 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 Merck Sharp & Dohme and Roche; 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. MK reports grants and personal fees from Actelion Pharmaceuticals; and personal fees from Bayer, Chugai, Corbus, CSL Behring and Reata Pharmaceuticals. YA reports grants and personal fees from Inventiva and Sanofi; and personal fees from Bayer, Boehringer Ingelheim, ChemomAb and Roche/Genentech. SA reports grants, personal fees and other support from Boehringer Ingelheim; grants from Bayer, Biogen and Momenta; and personal fees from Medscape and Integrity Continuing Education. AA reports personal fees and other support from Boehringer Ingelheim, Shionogi & Co., Ltd, and Taiho Pharmaceutical; and personal fees from Asahi Kasei Pharma. AB reports grants, personal fees, non-financial support and other support from Boehringer Ingelheim; personal fees, non-financial support and other support from Actelion Pharmaceuticals, AstraZeneca, Chiesi and Novartis;

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Data sharing statement

Information on data sharing is provided in the appendix.

Research in Context panel

Evidence before this study

We searched PubMed for all English-language papers published between January 1, 1990, and September 1, 2019, using the search terms "systemic sclerosis" and "nintedanib". Aside from the SENSCIS trial, we found no studies that investigated the efficacy of nintedanib in patients with SSc. In the SENSCIS trial, nintedanib reduced the annual rate of decline in FVC (mL/year) in patients with SSc-ILD by 44% vs placebo. Approximately half of the participants in this trial had been on stable therapy with mycophenolate for ≥6 months before randomisation. Nintedanib reduced the annual rate of decline in FVC both in patients who were and were not taking mycophenolate at baseline, with no heterogeneity detected in its treatment effect between the subgroups by mycophenolate use at baseline. The absolute effect of nintedanib vs placebo on reducing the rate of FVC decline was numerically lower in patients who were than were not taking mycophenolate at baseline (26.3 versus 55.4 mL/year), but the relative treatment effect of nintedanib was similar (40% and 46%, respectively).

Added value of this study

In this paper, we demonstrate that nintedanib provided benefits versus placebo on categorical declines in FVC both in patients who were and were not taking mycophenolate at baseline. In both the subgroups by mycophenolate use at baseline, a smaller proportion of patients treated with nintedanib than placebo had a decline in FVC of ≥3.3% predicted, which has been estimated as the MCID for worsening of FVC in patients with SSc-ILD. Further we demonstrate that the adverse event profile of nintedanib was similar between subgroups by mycophenolate use at baseline and was manageable for most patients. Treatment discontinuations due to adverse events over 52 weeks were not more common in patients treated with nintedanib and mycophenolate than in patients treated with nintedanib alone.

Implications of all the available evidence

Given the frequent use of mycophenolate in patients with SSc-ILD, these data provide important information on the potential concomitant use of nintedanib and mycophenolate in patients with SSc-ILD.

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Table 1. Baseline characteristics of patients in the SENSCIS trial in subgroups by use of mycophenolate at baseline

Characteristic	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Female	102 (73.4%)	101 (72.1%)	119 (79.9%)	111 (75.0%)
Age (years)	52.6 (12.0)	51.5 (11.9)	56.5 (11.3)	55.1 (13.0)
Body mass index (kg/m$^{2)}$	26.9 (5.0)	26.2 (5.5)	25.1 (4.5)	25.4 (4.8)
Race*				
White	112 (80.6%)	108 (77.1%)	89 (59.7%)	78 (52.7%)
Asian	9 (6.5%)	19 (13.6%)	53 (35.6%)	62 (41.9%)
Black/African-American	14 (10.1%)	9 (6.4%)	6 (4.0%)	7 (4.7%)
American Indian/Alaska Native/Native Hawaiian/other Pacific Islander	3 (2.2%)	2 (1.4%)	0 (0.0%)	1 (0.7%)
Region				
Europe	64 (46.0%)	58 (35.7%)	76 (51.0%)	68 (45.9%)
US and Canada	57 (41.0%)	57 (40.7%)	12 (8.1%)	16 (10.8%)
Asia	7 (5.0%)	12 (8.6%)	52 (34.9%)	59 (39.9%)
Rest of world	11 (7.9%)	13 (9.3%)	9 (6.0%)	5 (3.4%)
Diffuse cutaneous SSc	79 (56.8%)	74 (52.9%)	74 (49.7%)	72 (48.6%)
Years since onset of first non-Raynaud symptom	3.4 (0.9, 6.9)	3.5 (1.0, 7.0)	3.4 (0.3, 7.1)	3.3 (0.4, 7.2)
Extent of fibrotic ILD on HRCT (%)	37.9 (22.4)	35.8 (20.9)	35.8 (21.2)	34.7 (20.6)
FVC				
mL	2496 (724)	2581 (813)	2423 (748)	2503 (819)
% predicted	70.4 (15.6)	71.1 (16.5)	74.2 (17.7)	74.2 (16.6)
DL_{CO} % predicted†	50.8 (13.7)	52.6 (14.6)	54.8 (16.1)	53.8 (15.5)

Anti-topoisomerase I antibody positive	88 (62.9%)	84 (60.4%)	89 (59.7%)	89 (60.1%)
mRSS	12.5 (9.4)	11.3 (8.3)	10.3 (8.9)	10.5 (9.2)
SGRQ total score	43.9 (20.3)	41.1 (19.8)	38.0 (19.7)	37.8 (21.9)
C-reactive protein, mg/L‡	4.9 (5.9)	8.5 (25.3)	6.8 (15.3)	5.2 (7.7)
Platelets, 10^{-9}/L§	277 (79)	283 (77)	267 (77)	260 (73)

Data are n (%), mean (SD) or median (minimum, maximum).

*Data from patients who selected one race. Four patients ticked more than one box. †Corrected for haemoglobin.

‡Upper limit of normal reference range: 4.99mg/L. §Reference range 130-400 x 10^{-9}/L.

Table 2. Outcomes in subgroups by use of mycophenolate at baseline

	Patients taking mycophenolate at baseline		**Patients not taking mycophenolate at baseline**	
	Nintedanib	**Placebo**	**Nintedanib**	**Placebo**
Primary endpoint				
Annual rate of decline in FVC over 52 weeks (mL/year)	-40.2 (19.8)	-66.5 (19.3)	-63.9 (19.3)	-119.3 (19.0)
Difference (95% CI)	26.3 (-27.9, 80.6)		55.4 (2.3, 108.5)	
Treatment-by-time-by-subgroup interaction	p=0.45*			
Key secondary endpoints				
Absolute change from baseline in mRSS at week 52	-2.4 (0.4)	-2.5 (0.4)	-1.9 (0.4)	-1.5 (0.4)
Difference (95% CI)	0.04 (-1.01, 1.09)		-0.44 (-1.47, 0.58)	
Treatment-by-visit-by subgroup interaction	p=0.52			
Absolute change from baseline in SGRQ total score at week 52	0.7 (1.3)	-0.9 (1.2)	0.9 (1.2)	-0.9 (1.2)
Difference (95% CI)	1.6 (-1.9, 5.0)		1.8 (-1.6, 5.2)	
Treatment-by-visit-by subgroup interaction	p=0.92			
Other lung function endpoints				
Absolute change from baseline in FVC (mL) at week 52	-42.2 (20.0)	-78.6 (19.4)	-66.4 (19.4)	-122.7 (19.1)
Difference (95% CI)	36.43 (-18.3, 91.2)		56.3 (2.8, 109.7)	
Treatment-by-visit-by-subgroup interaction	p=0.61			

Annual rate of decline in FVC % predicted	-0.9 (0.6)	-1.7 (0.5)	-1.9 (0.5)	-3.4 (0.5)
Difference (95% CI)	0.8 (-0.7, 2.3)		1.5 (0.1, 3.0)	
Treatment-by-time-by-subgroup interaction	p=0.49			
Patients with an absolute decline from baseline in FVC of >5% predicted at week 52 — no./total no. (%)	21/138 (15.2)	36/140 (25.7)	38/149 (25.5)	46/148 (31.1)
Odds ratio (95% CI)	0.52 (0.29, 0.95)		0.76 (0.46, 1.26)	
Treatment−by−subgroup interaction	p=0.35			
Patients with an absolute decline from baseline in FVC of >10% predicted at week 52 — no./total no. (%)	4/138 (2.9)	7/140 (5.0)	16/149 (10.7)	17/148 (11.5)
Odds ratio (95% CI)	0.57 (0.16, 1.98)		0.93 (0.45, 1.91)	
Treatment−by−subgroup interaction	p=0.50			
Patients with a relative decline from baseline in FVC (mL) of >5% at week 52 — no./total no. (%)	39/138 (28.3)	57/140 (40.7)	56/149 (37.6)	68/148 (45.9)
Odds ratio (95% CI)	0.58 (0.35, 0.95)		0.71 (0.45, 1.13)	
Treatment−by−subgroup interaction	p=0.55			
Patients with a relative decline from baseline in FVC (mL) of >10% at week 52 — no./total no. (%)	14/138 (10.1)	21/140 (15.0)	34/149 (22.8)	31/148 (20.9)
Odds ratio (95% CI)	0.64 (0.31, 1.32)		1.12 (0.64, 1.94)	
Treatment−by−subgroup interaction	p=0.23			

*Difference in treatment effect between patients who were taking and not taking mycophenolate use at baseline: 29.1 mL (95% confidence interval: -46.8, 105.0). Changes from baseline are adjusted means (SE) based on the statistical models. FVC endpoints were analysed in 138 and 140 patients in the nintedanib and placebo groups, respectively, who were taking mycophenolate at baseline and 149 and 148 patients in these groups, respectively, who were not taking mycophenolate at baseline, except for the absolute change from baseline in FVC in mL, which was

analysed in 139 patients in the nintedanib group who were taking mycophenolate at baseline. Modified Rodnan skin score was analysed in 139 patients in the nintedanib and placebo groups who were taking mycophenolate at baseline and 149 and 147 patients in these groups, respectively, who were not taking mycophenolate at baseline. SGRQ total score was analysed in 137 and 138 patients in the nintedanib and placebo groups who were taking mycophenolate at baseline, and 145 patients in both groups who were not taking mycophenolate at baseline. FVC, forced vital capacity; mRSS, Modified Rodnan skin score; SGRQ, St George's Respiratory Questionnaire.

Table 3. Adverse events in subgroups by use of mycophenolate at baseline

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
Event	**Nintedanib (n=139)**	**Placebo (n=140)**	**Nintedanib (n=149)**	**Placebo (n=148)**
Any adverse event*	136 (97.8%)	135 (96.4%)	147 (98.7%)	141 (95.3%)
Most frequent adverse events†				
Diarrhoea	106 (76.3%)	48 (34.3%)	112 (75.2%)	43 (29.1%)
Nausea	43 (30.9%)	23 (16.4%)	48 (32.2%)	16 (10.8%)
Skin ulcer	22 (15.8%)	23 (16.4%)	31 (20.8%)	27 (18.2%)
Vomiting	32 (23.0%)	17 (12.1%)	39 (26.2%)	13 (8.8%)
Cough	20 (14.4%)	33 (23.6%)	14 (9.4%)	19 (12.8%)
Nasopharyngitis	10 (7.2%)	22 (15.7%)	26 (17.4%)	27 (18.2%)
Upper respiratory tract infection	19 (13.7%)	25 (17.9%)	14 (9.4%)	10 (6.8%)
Abdominal pain	14 (10.1%)	6 (4.3%)	19 (12.8%)	15 (10.1%)
Fatigue	19 (13.7%)	14 (10.0%)	12 (8.1%)	6 (4.1%)
Headache	16 (11.5%)	15 (10.7%)	11 (7.4%)	9 (6.1%)
Urinary tract infection	16 (11.5%)	11 (7.9%)	8 (5.4%)	12 (8.1%)
Weight decreased	10 (7.2%)	4 (2.9%)	24 (16.1%)	8 (5.4%)
Decreased appetite	14 (10.1%)	10 (7.1%)	13 (8.7%)	2 (1.4%)
Severe adverse event‡	28 (20.1%)	18 (12.9%)	24 (16.1%)	18 (12.2%)
Serious adverse event§	36 (25.9%)	22 (15.7%)	33 (22.1%)	40 (27.0%)
Fatal adverse event	3 (2.2%)	2 (1.4%)	2 (1.3%)	2 (1.4%)

Adverse event leading to treatment discontinuation	15 (10.8%)	9 (6.4%)	31 (20.8%)	16 (10.8%)

Data are n (%) of patients with ≥1 such adverse event.
* Adverse events reported over 52 weeks (or until 28 days after last trial drug intake for patients who discontinued trial drug before week 52)
†Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities. Adverse events reported in >10% of patients in any of these subgroups are shown.
‡Adverse event that was incapacitating or that caused an inability to work or to perform usual activities.
§Adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, 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.

Figure 1. Trial profile in subgroups by use of mycophenolate at baseline

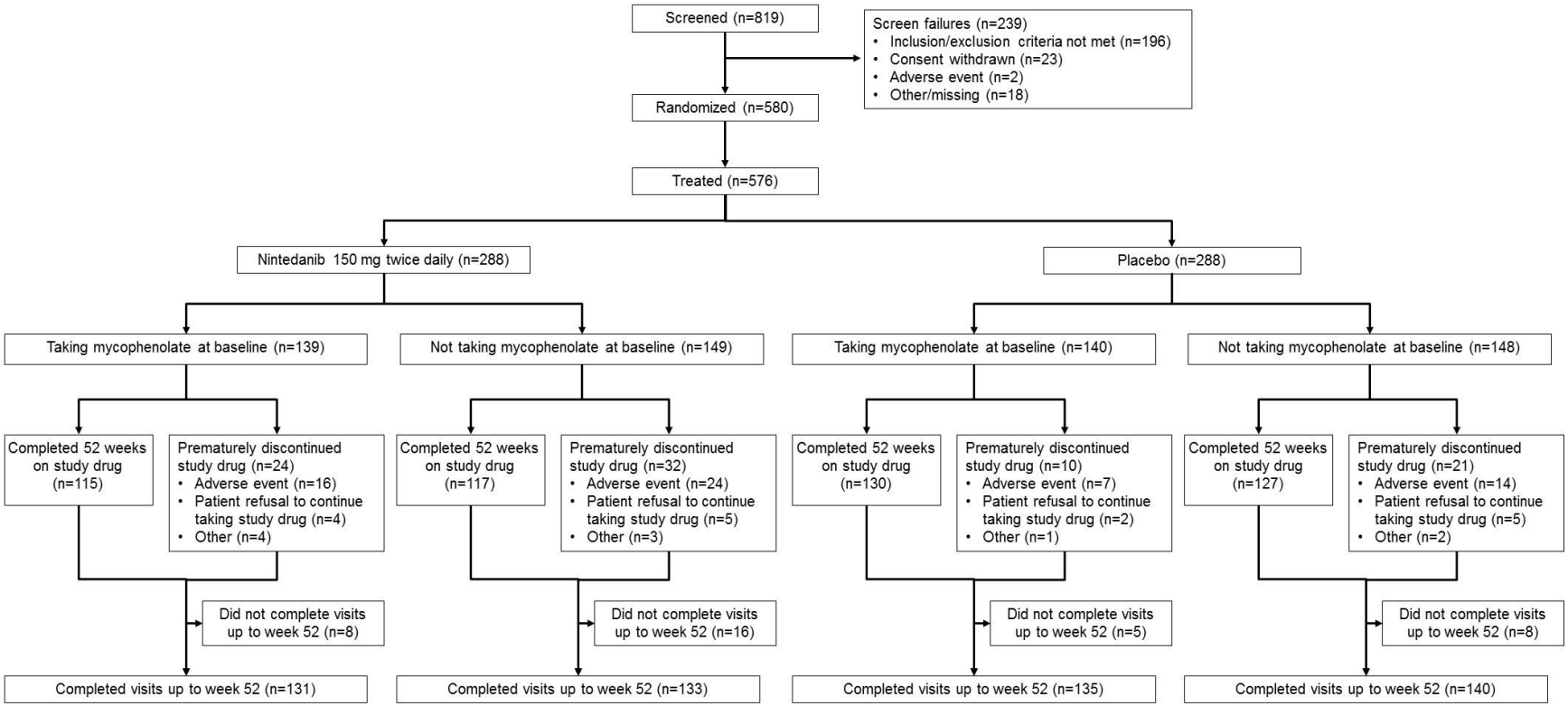
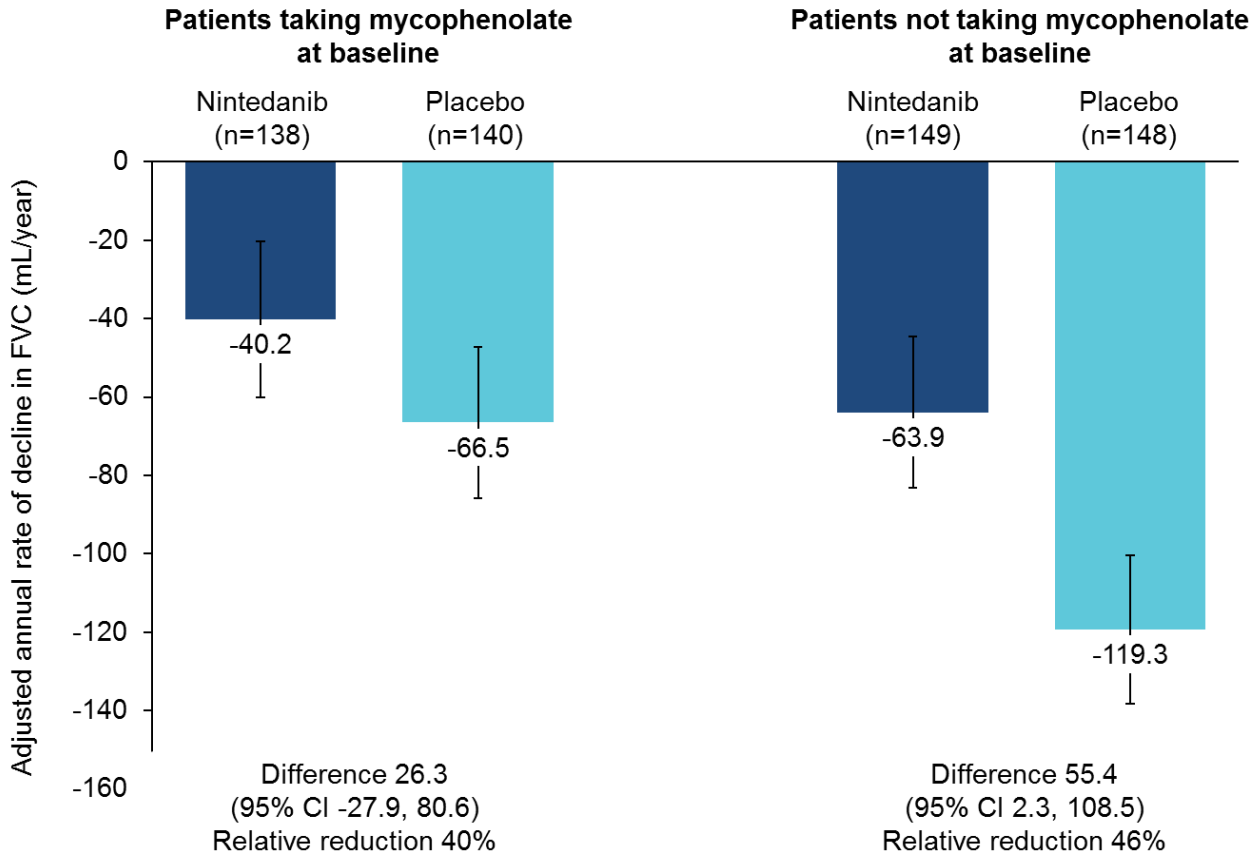


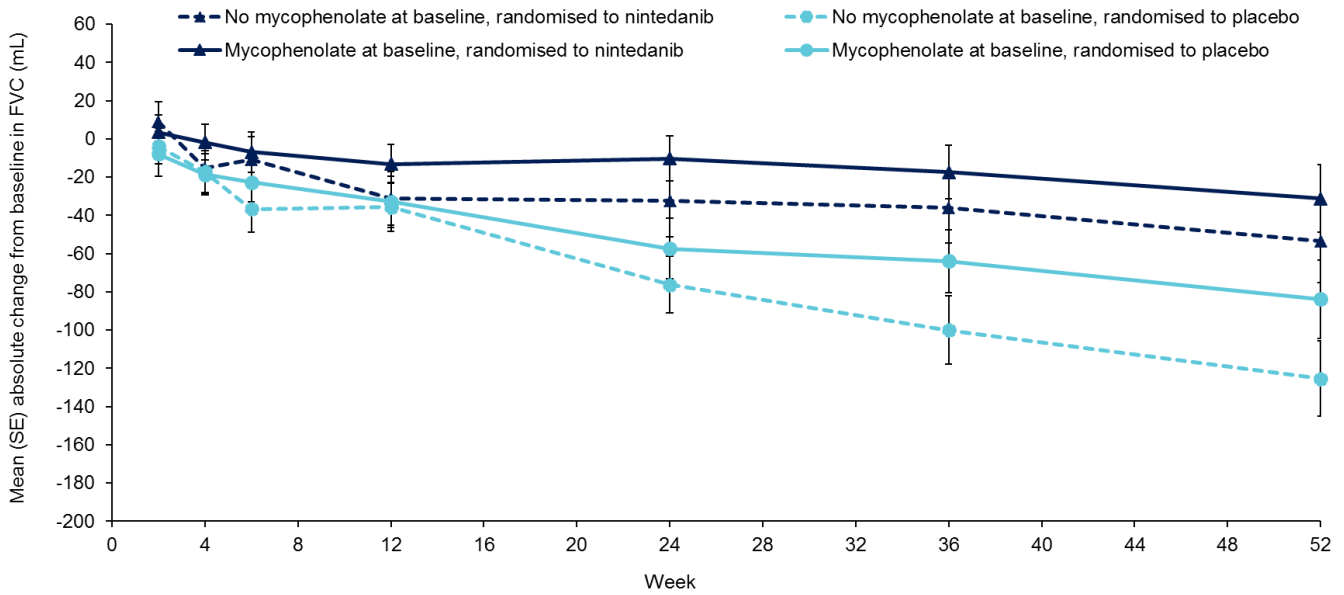
Figure 2. (A) Annual rate of decline in FVC (mL/year) over 52 weeks in subgroups by use of mycophenolate at baseline, **(B)** observed change from baseline in FVC (mL) over 52 weeks in subgroups by use of mycophenolate at baseline and **(C)** percentages of patients with an absolute increase from baseline in FVC of ≥3.0% predicted, stable FVC (absolute increase <3.0% predicted or decrease <3.3% predicted) and an absolute decrease in FVC of ≥3.3% predicted at week 52.

A



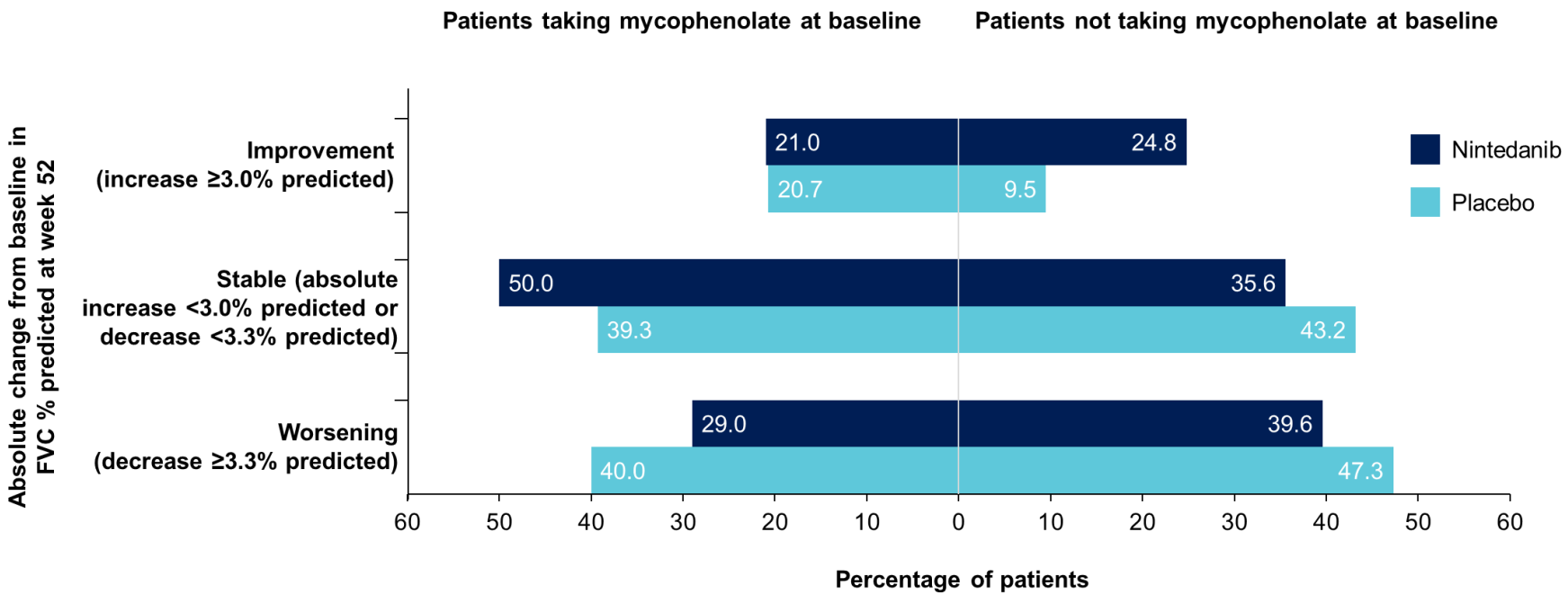
Random coefficient regression model including ATA status, age, height, sex and baseline FVC (ml) as covariates and terms for treatment-by-subgroup and treatment-by-subgroup-by-time interaction.
P-value for treatment-by-time-by-subgroup interaction = 0.45.

B



Number of patients							
Mycophenolate at baseline, randomised to nintedanib	138	134	131	135	129	128	116
No mycophenolate at baseline, randomised to nintedanib	145	147	142	143	136	134	125
Mycophenolate at baseline, randomised to placebo	136	139	139	139	137	133	127
No mycophenolate at baseline, randomised to placebo	147	142	141	144	143	135	130

C



Nintedanib: n=138 taking mycophenolate at baseline; n=149 not taking mycophenolate at baseline. Placebo: n=140 taking mycophenolate at baseline; n=148 not taking mycophenolate at baseline. Patients with improvement in FVC: p=0.01 for treatment−by−subgroup interaction; patients with stable FVC: p=0.03 for treatment−by−subgroup interaction; patients with worsening of FVC: p=0.62 for treatment−by−subgroup interaction.

Appendix

Eligibility criteria based on presence of SSc-ILD pattern and extent of fibrotic ILD on HRCT

A radiologist evaluated a patient's HRCT scan (performed ≤12 months before screening). The SSc-ILD pattern was assessed as described in the table below. The extent of fibrotic ILD was assessed visually in the whole lung to the nearest 5%. The assessment did not include pure (non-fibrotic) ground glass opacities.

Patients were considered for inclusion in the trial if the predominant features were consistent with an SSc-ILD pattern and the extent of fibrotic ILD was ≥10%. Patients were excluded if the predominant features were inconsistent with an SSc-ILD pattern and/or the extent of fibrotic ILD was <10% or 'unknown' was selected in the assessment of ILD pattern or extent due to image quality.

SSc-ILD assessment criteria

Pattern Assessment by HRCT	**SSc-ILD Pattern Description**
Features consistent with SSc-ILD pattern (text in bold represents common HRCT findings; note that not all features may be present in every subject; typical findings include GGO with superimposed fine IST/ILT and traction bronchiectasis; additional findings include oesophageal dilatation and enlarged mediastinal lymph nodes)	• **Ground glass opacity (GGO)** • **Honeycombing, traction bronchiectasis and bronchiolectasis, intralobular thickening (ILT), irregular interlobular septal thickening (IST), irregular interfaces** • **Posterior, peripheral and juxtapleural, and basal lung predominance** • **Pleural thickening or effusion** • Small centrilobular nodules (follicular bronchiolitis) **AND** • **Absence of features inconsistent with SSc-ILD (preferred); however, HRCT features inconsistent with SSc-ILD, in combination with predominant features consistent with SSc-ILD, will not result in exclusion of a subject from the study.**

Features inconsistent with SSc-ILD pattern	Any radiological features atypical of SSc-ILD that significantly impact the diagnosis of SSc-ILD on HRCT will be considered as inconsistent feature(s). These include, but are not limited to: • Mosaic attenuation (bilateral and/or multiple lobes) if it is predominant or if it is the only HRCT pattern [if the predominant pattern is consistent with fibrotic or cellular non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), the presence of mosaic attenuation will not lead to subject exclusion] • Air trapping (bilateral and/or multiple lobes) • Profuse micronodules (bilateral, predominant upper lobes) • Discrete cysts (multiple, bilateral away from honeycomb cysts).
Unknown	Image quality prevents an assessment

Statistical analysis

The rate of decline in FVC % predicted in subgroups by mycophenolate use at baseline was analysed using a random coefficient regression model (with random slopes and intercepts) including effects of baseline-by-time, ATA status (positive, negative), time, baseline FVC % predicted and treatment-by-subgroup and treatment-by-subgroup-by-time interactions.

The absolute change from baseline in FVC (mL) at week 52 in subgroups by mycophenolate use at baseline was analysed using a REML-based repeated measures approach including effects of ATA status (positive, negative), sex, age, height, and baseline-by-visit and treatment-by-subgroup-by-visit interactions.

The proportions of patients with an absolute increase in FVC of ≥3.0% predicted, stable FVC (absolute increase <3.0% predicted or decrease <3.3% predicted), an absolute decrease in FVC of ≥3.3% predicted, an absolute decline from baseline in FVC of >5% predicted, and an absolute decline from baseline in FVC of >10% predicted at week 52 were compared between treatment groups using a logistic regression model including treatment, ATA status (positive, negative), subgroup and treatment-by-subgroup interaction. Missing values were imputed using a worst value carried forward approach.

Mycophenolate use

At baseline, mycophenolate was taken by 80.3% of patients from US/Canada, 45.9% from Europe, and 14.6% from Asia. Data on the duration of prior mycophenolate use are available for 57 patients in the nintedanib group and 61 patients in the placebo group. The mean (SD) duration of prior mycophenolate use was 16.7 (12.5) months in the nintedanib group and 17.4 (14.9) months in the placebo group (median duration: 12.4 and 11.4 months, respectively). Data on the dose of mycophenolate used at baseline are available for 139 patients in the nintedanib group and 140 patients in the placebo group. In calculating the median dose, if a range of doses was entered on the case report form, the maximum dose was used and if a number of tablets was entered without further information, the dose was counted as 500 mg. The median (minimum, maximum) dose was 2000 (500, 26000) mg in the nintedanib group and 2000 (200, 4000) mg in the placebo group.

Of the patients taking mycophenolate at baseline, 131 of 139 (94%) patients in the nintedanib group and 136 of 140 (97%) patients in the placebo group were still taking mycophenolate at week 52.

Data sharing statement

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	The study will be publicly listed on https://vivli.org// in 2020.
Which data?	The anonymized clinical study data for the SENSCIS trial.
Additional information about data	
How or where can the data be obtained?	Interested researchers will be prompted to complete and submit a research proposal including a statistical analysis plan via https://vivli.org/. The submitted research proposal will be evaluated both by the sponsor, Boehringer Ingelheim, and also the Independent Review Panel. The Data Request Review Process is available at: https://vivli.org/ourmember/boehringer-ingelheim/
When will data availability begin?	Access to the data will be provided in a secure data access system, and upon the acceptance of the submitted research proposal, and governed by a data sharing agreement, and when the data have been anonymized.
When will data availability end?	An access period of 1 year is specified in the data sharing agreement, with the possibility of an extension, if required for a researcher to complete planned and submitted analysis, and upon a written agreement with Boehringer Ingelheim.
Will any supporting documents be available?	Supporting documents are also made available in the secure data access system when the data are shared.
Which supporting documents?	Redacted clinical trial reports, including the clinical trial protocol; the statistical analysis plan; the data specifications; and annotated case report forms.
Additional information about supporting documents	
How or where can supporting documents be obtained?	For approved data sharing requests: The corresponding documents are shared automatically with the data. For researchers who are interested in documents without requesting anonymized individual patient data: A request can be submitted, via https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html
When will supporting documents availability begin?	For data sharing requests: Upon the acceptance of the submitted research proposal, and governed by a data sharing agreement, and when the data have been anonymized. For documents without data requests: When the documents are redacted, and governed by a document sharing agreement.
When will supporting documents availability end?	For data sharing requests: An access period of 1 year is specified in the data sharing agreement, with the possibility of an extension, if required for a researcher to complete planned and submitted analysis, and upon a written agreement with Boehringer Ingelheim. For documents without data requests: Access is indefinite; the documents are securely transmitted directly to the researcher.
To whom will data be available?	To bona-fide researchers, who submit a research proposal form, and who have a statistician on the research team.

For what type of analysis or purpose?	The analysis must comply with patient informed consent.
By what mechanism?	The data are shared in a secure data access system.
Any other restrictions?	
Additional information	