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

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Summary

Background In the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, nintedanib reduced the rate of decline in forced vital capacity (FVC) in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). Patients on stable treatment with mycophenolate for at least 6 months before randomisation could participate. The aim of this subgroup analysis was to examine the efficacy and safety of nintedanib by mycophenolate use at baseline.

Methods The SENSCIS trial was a randomised, double-blind, placebo-controlled trial, in which patients with SSc-ILD were randomly assigned (1:1) to receive 150 mg of oral nintedanib twice daily or placebo for at least 52 weeks. In a prespecified subgroup analysis, we analysed the primary endpoint of rate of decline in FVC over 52 weeks by mycophenolate use at baseline. In a post-hoc analysis, we analysed the proportion of patients with an absolute decrease in FVC of at least 3·3% predicted at week 52 (proposed minimal clinically important difference estimate for worsening of FVC in patients with SSc-ILD) in subgroups by mycophenolate use at baseline. Adverse events were reported in subgroups by mycophenolate use at baseline. Analyses were done in all participants who received at least one dose of study drug. We analysed the annual rate of decline in FVC using a random coefficient regression model (with random slopes and intercepts) including anti-topoisomerase I antibody status, age, height, sex, and baseline FVC as covariates and terms for baseline-by-time, treatment-by-subgroup, and treatment-by-subgroup-by-time interactions. SENSCIS is registered with ClinicalTrials.gov, NCT02597933, and is now complete.

Findings Between Nov 30, 2015, and Oct 31, 2017, 819 participants were screened and 576 were enrolled, randomly assigned to, and treated with nintedanib (n=288) or placebo (n=288). 139 (48%) of 288 in the nintedanib group and 140 (49%) of 288 in the placebo group were taking mycophenolate at baseline. In patients taking mycophenolate at baseline, the adjusted mean annual rate of decline in FVC was –40·2 mL per year (SE 19·8) with nintedanib and –66·5 mL per year (19·3) with placebo (difference: 26·3 mL per year [95% CI –27·9 to 80·6]). In patients not taking mycophenolate at baseline, the adjusted mean annual rate of decline in FVC was –63·9 mL per year (SE 19·3) with nintedanib and –119·3 mL per year (19·0) with placebo (difference: 55·4 mL per year [95% CI 2·3 to 108·5]). We found no heterogeneity in the effect of nintedanib versus placebo on the annual rate of decline in FVC between the subgroups by mycophenolate use (p value for interaction=0·45). In a post-hoc analysis, the proportion of patients with an absolute decrease in FVC of at least 3·3% predicted was lower with nintedanib than with placebo in both patients taking mycophenolate (40 [29%] of 138 *vs* 56 [40%] of 140; odds ratio 0·61 [0·37 to 1·01]) and those not taking mycophenolate (59 [40%] of 149 *vs* 70 [47%] of 148; 0·73 [0·46 to 1·16]) at baseline. The adverse event profile of nintedanib was similar between the subgroups. Diarrhoea, the most common adverse event, was reported in 106 (76%) of 139 patients in the nintedanib group and 48 (34%) of 140 in the placebo group among those taking mycophenolate at baseline, and in 112 (75%) of 149 in the nintedanib group and 43 (29%) of 148 in the placebo group among those not taking mycophenolate at baseline. Over the entire trial period, 19 patients died (ten in the nintedanib group and nine in the placebo group). One death in the nintedanib group was considered to be related to study drug.

Interpretation Nintedanib reduced the progression of interstitial lung disease both in patients with SSc-ILD who were and were not using mycophenolate at baseline, with no heterogeneity in its treatment effect detected between the subgroups. The adverse event profile of nintedanib was similar in the subgroups by mycophenolate use. Our findings suggest that the combination of mycophenolate and nintedanib offers a safe treatment option for patients with SSc-ILD. More data are needed on the benefits of initial combination therapy versus a sequential approach to treatment of SSc-ILD.

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Research in context

Evidence before this study

We searched PubMed for papers published in English between Jan 1, 1990, and Sept 1, 2019, using the search terms "systemic sclerosis" AND "nintedanib". Aside from the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, we found no studies that investigated the efficacy of nintedanib in patients with systemic sclerosis. In the SENSCIS trial, nintedanib reduced the annual rate of decline in FVC (mL per year) in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) by 44% versus placebo. Approximately half of the participants in this trial had been on stable therapy with mycophenolate for at least 6 months before randomisation. The efficacy and safety of concomitant use of nintedanib and mycophenolate in patients with SSc-ILD had not been established.

Added value of this study

To our knowledge, in this subgroup analysis of the SENSCIS trial, we analysed the largest cohort of patients with SSc-ILD taking mycophenolate at baseline in a clinical trial to date. We did not detect heterogeneity in the effect of nintedanib versus placebo on the annual rate of decline in FVC between subgroups defined by mycophenolate use at baseline, which suggests that nintedanib provided benefits on decreases in FVC both in patients who were taking mycophenolate at baseline and in those who were not. In both of these subgroups, a smaller proportion of patients treated with nintedanib versus placebo had a decrease in FVC of at least 3·3% predicted, which has been estimated to be the minimum clinically important difference for worsening of FVC in patients with SSc-ILD. We found 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 who were on mycophenolate at baseline 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. More data are needed on the benefits of initial combination therapy versus a sequential approach to treatment of SSc-ILD.

Introduction

Systemic sclerosis is an autoimmune disease with heterogeneous organ manifestations.[1] Interstitial lung disease is a common manifestation and the leading cause of death in patients with systemic sclerosis.[2,3] A decline in forced vital capacity (FVC) is a predictor of mortality in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).[4,5] The mainstay of treatment for systemic sclerosis is immunosuppression. Based on the results of retrospective cohort studies[6] and the 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 one small (n=42) placebo-controlled trial of mycophenolate in patients with SSc-ILD has been done to date.[10]

Nintedanib is an intracellular inhibitor of tyrosine kinases that has shown antifibrotic, anti-inflammatory, and vascular remodelling effects in preclinical models of systemic sclerosis and interstitial lung disease.[11–14] Nintedanib is an approved treatment for idiopathic pulmonary fibrosis and SSc-ILD in many countries. In the phase 3 Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial, in patients with SSc-ILD, oral nintedanib 150 mg twice daily reduced the progression of interstitial lung disease, as shown by a reduction in the rate of decrease in FVC over 52 weeks, with an adverse event profile that was manageable for most patients and similar to that observed in patients with idiopathic pulmonary fibrosis, but with no significant benefit on skin fibrosis assessed with the modified Rodnan skin score (mRSS) or health-related quality of life measured using the St George's Respiratory Questionnaire (SGRQ).[15,16] Approximately half of the patients in the SENSCIS trial were taking a stable dose of mycophenolate at baseline, and the combination of nintedanib and mycophenolate is likely to be considered as a treatment option for patients with SSc-ILD. 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, phase 3 trial that was run in academic medical centres, hospitals, and private practices in 32 countries.[15] Eligibility criteria for the SENSCIS trial have been published elsewhere,[15,17] and the trial protocol and statistical analysis plan are publicly available.[15] Briefly, eligible patients had to be aged 18 years or older and have systemic sclerosis according to American College of Rheumatology–European League Against Rheumatism classification criteria[1] with onset of first non-Raynaud's symptom less than 7 years before screening. Interstitial lung disease was identified on the basis of a high-resolution CT scan done within 12 months before screening (appendix p 5). Patients also needed to

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See Online for appendix

have a fibrotic interstitial lung disease extent of at least 10%, confirmed by central assessment by an expert radiologist (National Jewish Health, Denver, CO, USA; appendix p 5), and an FVC of at least 40% predicted and a diffusing capacity of the lung for carbon monoxide (corrected for haemoglobin) of 30–89% predicted.

Patients receiving prednisone 10 mg per day or less, or stable therapy with mycophenolate or methotrexate for at least 6 months before randomisation could participate. Patients were not eligible to participate if they had been given a dose of prednisone of more than 10 mg per day (or equivalent) within 2 weeks before randomisation; azathioprine, hydroxychloroquine, colchicine, penicillamine, or sulfasalazine within 8 weeks before randomisation; or cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, ciclosporin, newer antiarthritic treatments (eg, tofacitinib), or potassium aminobenzoate within 6 months before randomisation.

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 an independent ethics committee or institutional review board at every site. All patients provided written informed consent. The protocol is available online.[15]

Randomisation and masking

After a screening period of 12 weeks or less, participants were randomly assigned (1:1), using a pseudo-random number generator, in block sizes of 4 and stratified by the presence of anti-topoisomerase I antibody, to receive oral nintedanib 150 mg twice daily or placebo. The study sponsor allocated participants using an interactive web-based response system. 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 (Dec 19, 2018). The success of masking was not assessed.

Procedures

Patients remained on masked treatment until the last patient had reached week 52, but for 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 at least 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.[15]

Outcomes

The primary endpoint was the annual rate of decline in FVC (mL per year) assessed over 52 weeks. Key secondary endpoints were absolute changes from baseline in mRSS and SGRQ total score at week 52. The mRSS assesses 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.[18] The SGRQ is a self-administered 50-item questionnaire, comprising three domains (symptoms, activity, impact), which assesses health-related quality of life in patients with respiratory disease.[19] Domain and total scores range from 0 to 100, with higher scores indicating worse health-related quality of life.

Other secondary endpoints included the annual rate of decline in % predicted FVC, the absolute change from baseline in FVC (mL) at week 52, the proportion of patients who had absolute decreases in FVC from baseline of more than 5% predicted and more than 10% predicted at week 52, and the proportion of patients who had relative declines in FVC (mL) from baseline of more than 5% and more than 10% at week 52. A full list of secondary endpoints can be found in the protocol.[15]

Assessments of the primary endpoint, key secondary endpoints, and adverse events in subgroups by use of mycophenolate at baseline were prespecified in the statistical analysis plan (before database lock and unmasking).[15] Assessment of the other endpoints listed above in subgroups by use of mycophenolate at baseline was post hoc. Post hoc, we also assessed the proportion of patients who had an absolute increase in FVC of at least 3·0% predicted, stable FVC (absolute increase of <3·0% predicted or decrease of <3·3% predicted), and an absolute decrease in FVC of at least 3·3% predicted at week 52; these post-hoc endpoints correspond to the proposed estimates for minimum clinically important difference for improvement in FVC, stable FVC, and worsening of FVC on the basis of 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).[20]

The proportion of patients who died was analysed over the entire trial period. Safety was assessed on the basis of adverse events reported, irrespective of causality, over 52 weeks (or until 28 days after last study 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). A severe adverse event was defined as an adverse event that was incapacitating or that caused an inability to work or do

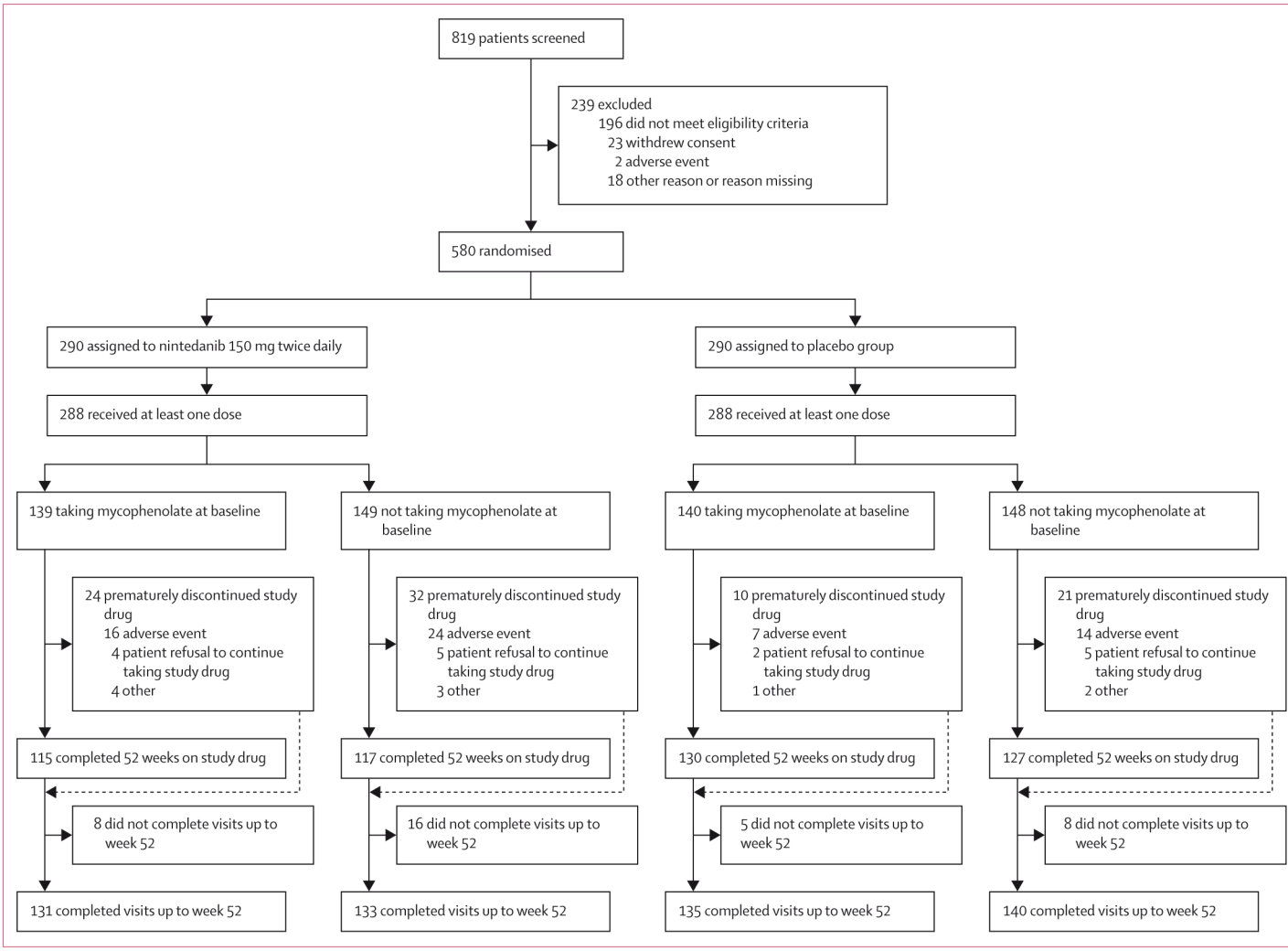

Figure 1: **Trial profile in subgroups by use of mycophenolate at baseline**
Four participants assigned to treatment did not receive at least one dose: three patients underwent randomisation but were not eligible and one withdrew consent.

usual activities. A serious adverse event was defined as an adverse event that resulted in death, was life-threatening, resulted in admission to hospital or extended stay in hospital, 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.

Statistical analysis

In the calculation of the sample size for the overall trial, the difference in the absolute change from baseline in FVC at week 52 between the trial groups was assumed to be 70 to 110 mL and a sample size of 260 patients per treatment group was estimated to provide 90% power to detect a between-group difference of 70 mL in the annual rate of decline in FVC.[15]

The analyses done in the full study population have been described previously.[15] Here we report the results of analyses in subgroups of participants by use of mycophenolate (mofetil or sodium) at baseline. All analyses were done in participants who received at least one dose of study drug. We analysed the annual rate of decline in FVC (mL per year) in the subgroups using a random coefficient regression model (with random slopes and intercepts) including anti-topoisomerase I antibody status (positive, negative), age, height, sex, and baseline FVC (mL) as covariates and terms for baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions. Time was defined as duration since the first intake of study drug and was used as a continuous variable in this analysis. The analysis was based on all measurements taken within the first 52 weeks of the study, including those from participants who discontinued study drug. The model allowed for missing data, assuming they were missing at random. We analysed changes from baseline in mRSS and SGRQ total score at week 52 in the subgroups using a restricted maximum likelihood-based

repeated measures approach. The analyses included fixed categorical effects of anti-topoisomerase I antibody status (positive, negative), visit, and treatment-by-subgroup-by-visit interaction, and fixed continuous effect of baseline by visit. We used a least squares mean estimate statement, with appropriate contrasts, to do 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. In the analysis of categorical changes in FVC (% predicted or mL) at week 52, data from participants with missing values at week 52 were imputed using a worst-value-carried-forward approach; we assumed that missing FVC data at week 52 were missing at random because most 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 (p 6). We present the adverse events by subgroup using descriptive statistics.

We used SAS (version 9.4) for all analyses. SENSCIS is registered with ClinicalTrials.gov, NCT02597933.

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Sex				
Female	102 (73%)	101 (72%)	119 (80%)	111 (75%)
Male	37 (27%)	39 (28%)	30 (20%)	37 (25%)
Age, years	52·6 (12·0)	51·5 (11·9)	56·5 (11·3)	55·1 (13·0)
Body-mass index, kg/m²	26·9 (5·0)	26·2 (5·5)	25·1 (4·5)	25·4 (4·8)
Race*				
White	112 (81%)	108 (77%)	89 (60%)	78 (53%)
Asian	9 (6%)	19 (14%)	53 (36%)	62 (42%)
Black or African-American	14 (10%)	9 (6%)	6 (4%)	7 (5%)
American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander	3 (2%)	2 (1%)	0	1 (1%)
Region				
Europe	64 (46%)	58 (41%)	76 (51%)	68 (46%)
USA and Canada	57 (41%)	57 (41%)	12 (8%)	16 (11%)
Asia	7 (5%)	12 (9%)	52 (35%)	59 (40%)
Rest of world	11 (8%)	13 (9%)	9 (6%)	5 (3%)
Diffuse cutaneous SSc	79 (57%)	74 (53%)	74 (50%)	72 (49%)
Years since onset of first non-Raynaud's 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 high-resolution CT, %	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)
Diffusing capacity of the lung for carbon monoxide, % predicted†	50·8 (13·7)	52·6 (14·6)	54·8 (16·1)	53·8 (15·5)
Anti-topoisomerase I antibody positive	88 (63%)	84 (60%)	89 (60%)	89 (60%)
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 per L§	277 (79)	283 (77)	267 (77)	260 (73)

Data are n (%), mean (SD), or median (minimum–maximum). FVC=forced vital capacity. ILD=interstitial lung disease. mRSS=modified Rodnan skin score. SENSCIS=Safety and Efficacy of Nintedanib in Systemic Sclerosis. SGRQ=St George's Respiratory Questionnaire. SSc=systemic sclerosis. *Data from patients who selected one race; four patients ticked more than one box. †Corrected for haemoglobin. ‡Upper limit of normal reference range: 4·99 mg/L. §Reference range 130–400 × 10^9 per L.

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

Role of the funding source

The funder participated in the study design, data collection, data analysis, 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

Between Nov 30, 2015, and Oct 31, 2017, 819 patients were screened and 580 were randomly assigned to either nintedanib (290) or placebo (290). 576 patients received at least one dose of nintedanib (288) or placebo (288; figure 1). At baseline, 139 (48%) participants in the nintedanib group and 140 (49%) in the placebo group were taking mycophenolate (268 [47%] mycophenolate mofetil, 11 [2%] mycophenolate sodium). The median dose of mycophenolate used at baseline was 2000 mg (minimum 500, maximum 2600) in the nintedanib group, and 2000 mg (minimum 200, maximum 4000) in the placebo group (more information on mycophenolate use is in the appendix [p 7]). Mean age and sex distributions were similar across subgroups (table 1). The proportion of participants with diffuse cutaneous systemic sclerosis was higher among those who were taking mycophenolate at baseline than in those not taking mycophenolate at baseline. Also, mean mRSS was higher and mean FVC % predicted was lower in those taking mycophenolate at baseline than in those not taking mycophenolate at baseline (table 1). Of the participants who were taking mycophenolate at baseline, 131 (94%) of 139 in the nintedanib group and 136 (97%) of 140 in the placebo group were still taking mycophenolate at week 52. Only 11 (4%) of 297 participants (five in the nintedanib group and six in the placebo group) who were not taking mycophenolate at baseline started mycophenolate during the 52 weeks of trial treatment. 20 (7%) patients in the group that did not take mycophenolate at baseline started therapies that were restricted at randomisation during the 52 weeks of trial treatment. A post-baseline FVC measurement was not available for one patient, so for relevant analyses only 138 participants in this group are included.

In both subgroups by mycophenolate use, a smaller proportion of participants randomly assigned to the

nintedanib group completed 52 weeks of treatment (115 [83%] of those taking mycophenolate, 117 [79%] of those not taking mycophenolate) than did those assigned to the placebo group (130 [93%] of those taking mycophenolate and 127 [86%] of those not taking mycophenolate). Mean exposure to trial medication over 52 weeks was slightly lower among participants in the nintedanib group who were (10·7 months [SD 3·3]) and

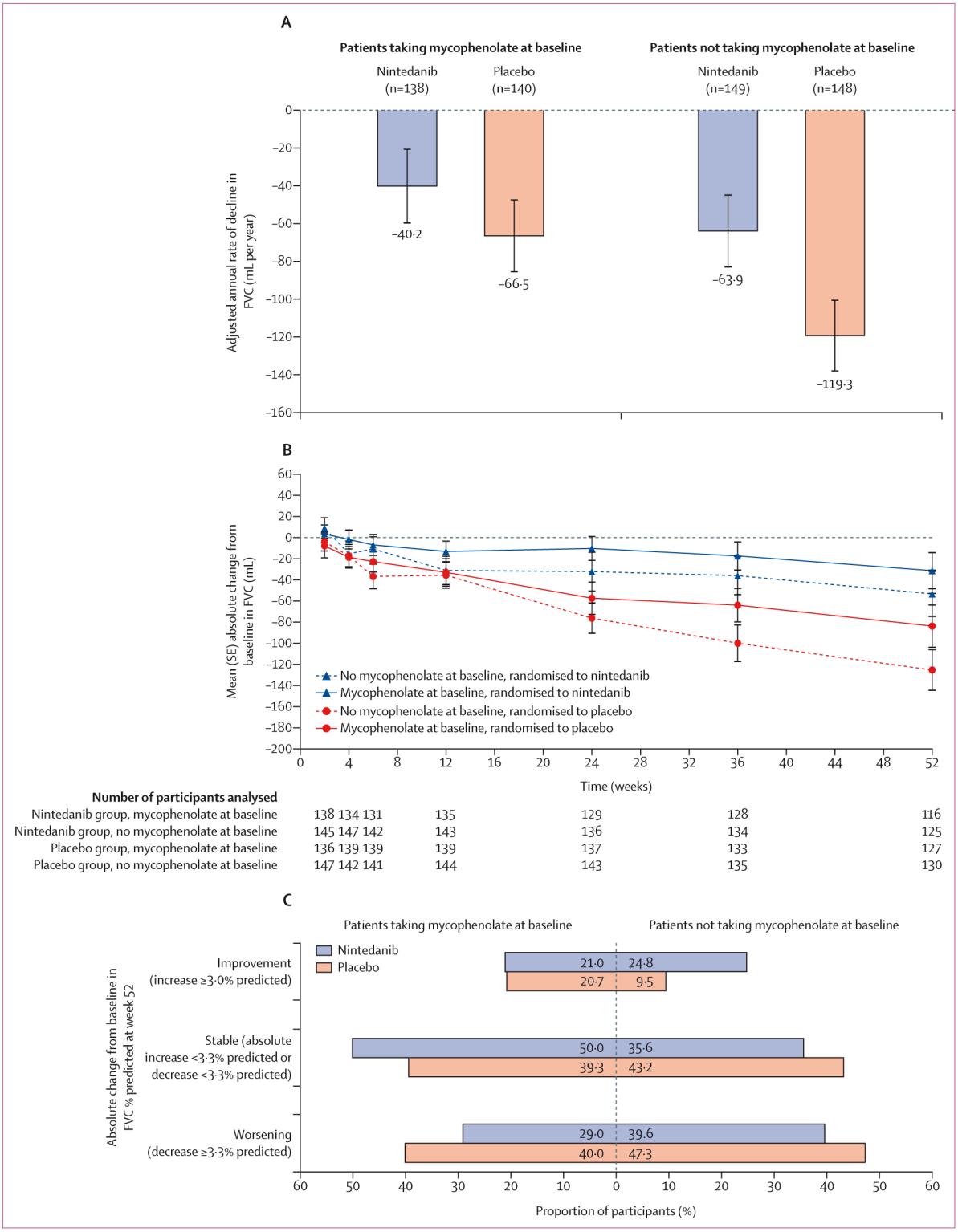

Figure 2: **Annual rate of decline in FVC (mL per year) over 52 weeks (A), observed change from baseline in FVC (mL) over 52 weeks (B), and proportion of participants who had improvement in FVC, stable FVC, and worsening of FVC between baseline and week 52 (post-hoc analysis; C), in subgroups by use of mycophenolate at baseline**
In part A, random coefficient regression model including anti-topoisomerase I antibody 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 was 0·45. 138 of 139 participants in the nintedanib group who were taking mycophenolate at baseline were analysed; a post-baseline FVC measurement was not available for one patient. In panel C, analysable population was 138 in the nintedanib group taking mycophenolate at baseline and 149 not taking mycophenolate at baseline, and 140 in the placebo group taking mycophenolate at baseline and 148 not taking mycophenolate at baseline. Patients with improvement in FVC: p=0·011 for treatment-by-subgroup interaction; patients with worsening of FVC: p=0·62 for treatment-by-subgroup interaction. FVC=forced vital capacity.

were not taking mycophenolate at baseline (10·3 months [3·6]) than among those in the placebo group (11·6 months [2·0] and 11·1 months [2·7]).

Compared with placebo, nintedanib was associated with a reduced annual rate of decline in FVC in both the subgroup of patients taking mycophenolate at baseline and the subgroup not taking mycophenolate at baseline (figure 2, 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 2). The treatment effect of nintedanib on the annual rate of FVC decline was numerically greater in participants who were not taking mycophenolate at baseline (difference: 55·4 mL per year [95% CI 2·3 to 108·5]) than in those who were taking mycophenolate (26·3 mL per year [–27·9 to 80·6]; table 2), corresponding to a relative reduction of 46% in the non-mycophenolate group and 40% in the mycophenolate group compared with placebo. 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 (difference 41·0 mL per year [95% CI 2·9 to 79·0]; p=0·04).[15]

In the overall population, no significant difference was seen between nintedanib and placebo for change from baseline in mRSS (difference –0·21 [95% CI –0·94 to 0·53]) or SGRQ total score (1·69 [–0·73 to 4·12]) at week 52.[15] In our subgroup analyses, 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).

Absolute decrease in FVC of more than 5% predicted was seen in 21 (15%) of 138 participants in the nintedanib group and 36 (26%) of 140 participants in the placebo group who were taking mycophenolate at baseline, and in 38 (26%) of 149 in the nintedanib group and 46 (31%) of 148 in the placebo group not taking mycophenolate at baseline. Absolute decrease in FVC of more than 10% predicted was seen in four (3%)

	Patients taking mycophenolate at baseline				Patients not taking mycophenolate at baseline				p value for interaction
	Nintedanib (n=139)	Placebo (n=140)	Difference	Odds ratio	Nintedanib (n=149)	Placebo (n=148)	Difference	Odds ratio	
Primary endpoint									
Adjusted annual rate of decline in FVC over 52 weeks, mL per year	−40·2 (19·8)	−66·5 (19·3)	26·3 (−27·9 to 80·6)	..	−63·9 (19·3)	−119·3 (19·0)	55·4 (2·3 to 108·5)	..	0·45*†
Key secondary endpoints									
Adjusted absolute change from baseline in mRSS at week 52	−2·4 (0·4)	−2·5 (0·4)	0·04 (−1·01 to 1·09)	..	−1·9 (0·4)	−1·5 (0·4)	−0·44 (−1·47 to 0·58)	..	0·52‡
Adjusted absolute change from baseline in SGRQ total score at week 52	0·7 (1·3)	−0·9 (1·2)	1·6 (−1·9 to 5·0)	..	0·9 (1·2)	−0·9 (1·2)	1·8 (−1·6 to 5·2)	..	0·92‡
Other secondary lung function endpoints									
Adjusted change from baseline in FVC at week 52, mL	−42·2 (20·0)	−78·6 (19·4)	36·43 (−18·3 to 91·2)	..	−66·4 (19·4)	−122·7 (19·1)	56·3 (2·8 to 109·7)	..	0·61‡
Annual rate of decline in FVC % predicted	−0·9 (0·6)	−1·7 (0·5)	0·8 (−0·7 to 2·3)	..	−1·9 (0·5)	−3·4 (0·5)	1·5 (0·1 to 3·0)	..	0·49†
Patients with an absolute decrease from baseline in FVC of >5% predicted at week 52	21/138 (15%)	36/140 (26%)	..	0·52 (0·29 to 0·95)	38/149 (26%)	46/148 (31%)	..	0·76 (0·46 to 1·26)	0·35§
Patients with an absolute decrease from baseline in FVC of >10% predicted at week 52	4/138 (3%)	7/140 (5%)	..	0·57 (0·16 to 1·98)	16/149 (11%)	17/148 (12%)	..	0·93 (0·45 to 1·91)	0·50§
Patients with a relative decrease from baseline in FVC (mL) of >5% at week 52	39/138 (28%)	57/140 (41%)	..	0·58 (0·35 to 0·95)	56/149 (38%)	68/148 (46%)	..	0·71 (0·45 to 1·13)	0·55§
Patients with a relative decrease from baseline in FVC (mL) of >10% at week 52	14/138 (10%)	21/140 (15%)	..	0·64 (0·31 to 1·32)	34/149 (23%)	31/148 (21%)	..	1·12 (0·64 to 1·94)	0·23§

Data are mean (SE), n/N (%), difference (95% CI), or odds ratio (95% CI). Changes from baseline are adjusted means (SE) based on the statistical models. FVC endpoints were analysed in 138 participants in the nintedanib group (a post-baseline FVC measurement was not available for one patient) and 140 participants in the placebo group who were taking mycophenolate at baseline and 149 in the nintedanib group and 148 in the placebo group 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. mRSS was analysed in 139 patients in the nintedanib and placebo groups who were taking mycophenolate at baseline and 149 in the nintedanib group and 147 in the placebo group who were not taking mycophenolate at baseline. SGRQ total score was analysed in 137 patients in the nintedanib group and 138 in the placebo group 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. *Difference in treatment effect between patients who were taking and not taking mycophenolate use at baseline: 29·1 mL (95% CI −46·8 to 105·0). †Treatment-by-time-by-subgroup interaction. ‡Treatment-by-visit-by-subgroup interaction. §Treatment-by-subgroup interaction.

Table 2: **Outcomes in subgroups by use of mycophenolate at baseline**

participants in the nintedanib group and seven (5%) in the placebo group taking mycophenolate at baseline, and in 16 (11%) participants in the nintedanib group and 17 (11%) in the placebo group not taking mycophenolate at baseline (table 2). Post-hoc analyses of annual rate of decline in % predicted FVC and absolute change from baseline in FVC (mL) at week 52 in subgroups by mycophenolate use at baseline are shown in table 2.

In our post-hoc analyses, the proportion of patients with an absolute increase in FVC of at least 3·0% predicted at week 52 was similar between participants in the nintedanib and placebo groups taking mycophenolate at baseline (29 [21%] of 138 *vs* 29 [21%] of 140; odds ratio [OR] 1·01 [95% CI 0·57–1·81]) but greater with nintedanib than placebo in those not taking mycophenolate at baseline (37 [25%] of 149 *vs* 14 [10%] of 148; 3·17 [1·63–6·16]; figure 2). The proportion of patients with an absolute decrease in FVC of at least 3·3% predicted was lower with nintedanib than with placebo in those taking mycophenolate at baseline (40 [29%] of 138 *vs* 56 [40%] of 140; 0·61 [0·37–1·01]) and not taking mycophenolate at baseline (59 [40%] of 149 *vs* 70 [47%] of 148; 0·73 [0·46–1·16]; figure 2). The proportion of patients with stable FVC at week 52 was greater with nintedanib than with placebo in those taking mycophenolate at baseline (69 [50%] of 138 *vs* 55 [39%] of 140; OR 1·54 [95% CI 0·96–2·49]) but similar between nintedanib and placebo groups in those not taking mycophenolate at baseline (53 [36%] of 149 *vs* 64 [43%] of 148; OR 0·72 [0·45–1·16]; figure 2).

The adverse event profile of nintedanib was generally similar in the subgroups by mycophenolate use (table 3). Adverse events that led to discontinuation of treatment occurred in 15 (11%) of 139 participants in the nintedanib group and nine (6%) of 140 in the placebo group who were taking mycophenolate at baseline, and in 31 (21%) of 149 in the nintedanib group and 16 (11%) of 148 in the placebo group who were not mycophenolate at baseline. The most frequent adverse event reported was diarrhoea. In the nintedanib group, diarrhoea led to treatment discontinuation in seven (5%) patients who were taking mycophenolate at baseline and 13 (9%) patients who were not taking mycophenolate at baseline; and in the placebo group, diarrhoea led to treatment discontinuation in one (1%) patient who was taking mycophenolate at baseline and in no patients who were not taking mycophenolate at baseline. Serious diarrhoea adverse events were reported for two (1%) patients in the nintedanib group and one (1%) patient in the placebo group who were taking mycophenolate at baseline, and no patients in the ninedanib group and one (1%) patient in the placebo group who were not taking mycophenolate at baseline. Of the 106 participants in the nintedanib group who were taking mycophenolate at baseline and had at least one diarrhoea adverse event, 73 (69%) had one or two events, ten (9%) had three events, and 23 (22%) had four or more events. 97 (92%) of these 106 patients had diarrhoea events that were at worst of mild or moderate intensity, 32 (30%) had events that led to permanent dose reduction, and seven (7%) had events that led to treatment discontinuation. Of the 112 patients in the nintedanib group who were not taking mycophenolate at baseline and had at least one diarrhoea adverse event, 80 (71%) had one or two events, 14 (13%) had three events, and 18 (16%) had four or more events. 109 (97%) of these 112 patients had diarrhoea events that were at worst of mild or moderate intensity, 25 (22%) had events that led to permanent dose reduction, and 13 (12%) had events that led to treatment discontinuation.

Abdominal pain was reported in 14 (10%) participants in the nintedanib group and six (4%) in the placebo group who were taking mycophenolate at baseline, and in 19 (13%) in the nintedanib group and 15 (10%) in the placebo group who were not taking mycophenolate at baseline (table 3). A decrease in weight was recorded in ten (7%) participants in the nintedanib group and four (3%) in the placebo group who were taking mycophenolate at baseline, and in 24 (16%) in the nintedanib group and eight (5%) in the placebo group who were not taking mycophenolate at baseline. The proportions of participants with upper respiratory tract infection, fatigue, cough, and headache were higher

	Patients taking mycophenolate at baseline		Patients not taking mycophenolate at baseline	
	Nintedanib (n=139)	Placebo (n=140)	Nintedanib (n=149)	Placebo (n=148)
Any adverse event*	136 (98%)	135 (96%)	147 (99%)	141 (95%)
Most frequent adverse events†				
Diarrhoea	106 (76%)	48 (34%)	112 (75%)	43 (29%)
Nausea	43 (31%)	23 (16%)	48 (32%)	16 (11%)
Skin ulcer	22 (16%)	23 (16%)	31 (21%)	27 (18%)
Vomiting	32 (23%)	17 (12%)	39 (26%)	13 (9%)
Cough	20 (14%)	33 (24%)	14 (9%)	19 (13%)
Nasopharyngitis	10 (7%)	22 (16%)	26 (17%)	27 (18%)
Upper respiratory tract infection	19 (14%)	25 (18%)	14 (9%)	10 (7%)
Abdominal pain	14 (10%)	6 (4%)	19 (13%)	15 (10%)
Fatigue	19 (14%)	14 (10%)	12 (8%)	6 (4%)
Headache	16 (12%)	15 (11%)	11 (7%)	9 (6%)
Urinary tract infection	16 (12%)	11 (8%)	8 (5%)	12 (8%)
Weight decreased	10 (7%)	4 (3%)	24 (16%)	8 (5%)
Decreased appetite	14 (10%)	10 (7%)	13 (9%)	2 (1%)
Severe adverse event	28 (20%)	18 (13%)	24 (16%)	18 (12%)
Serious adverse event	36 (26%)	22 (16%)	33 (22%)	40 (27%)
Fatal adverse event	3 (2%)	2 (1%)	2 (1%)	2 (1%)
Adverse event leading to treatment discontinuation	15 (11%)	9 (6%)	31 (21%)	16 (11%)

Data are n (%) of patients with at least one such adverse event. *Adverse events reported over 52 weeks (or until 28 days after last study drug intake for patients who discontinued study drug before week 52). †Adverse events that were reported in >10% of participants in any of these subgroups are shown.

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

among those 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 (ten in the nintedanib group and nine in the placebo group), of whom six (four in the nintedanib group and two in the placebo group) were taking mycophenolate at baseline. In the placebo group, adjudicated causes of death by MedDRA preferred terms were cardiac arrest (two patients), acute myocardial infarction (one), interstitial lung disease (one), pneumonia, dyspnoea (one), septic shock (one), sudden death (one), and lung neoplasm malignant (one). In the nintedanib group, adjudicated causes of death by MedDRA preferred terms were lung adenocarcinoma (one patient), thrombotic microangiopathy and scleroderma renal crisis (one), mesothelioma malignant (one), arrhythmia (one), pneumonia (one), acute lung injury (considered related to study drug; one), respiratory failure (one), chest pain (one), small-cell lung cancer (one), and circulatory collapse (one).

Discussion

To our knowledge, the SENSCIS trial is the largest clinical trial to have been done 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 included in a clinical trial to date. No heterogeneity was detected in the effect of nintedanib versus placebo in reducing the rate of decline in FVC (mL per year) over 52 weeks between prespecified subgroups by use of mycophenolate at baseline. Although the absolute effect of nintedanib versus placebo on reducing the rate of decline in FVC was numerically lower in participants who were taking mycophenolate at baseline than in those who were not, the relative treatment effect of nintedanib was similar between these subgroups (40% for those taking mycophenolate at baseline and 46% for those not taking mycophenolate at baseline) and consistent with that observed in the overall population (44%).[15] As observed in the overall population, no benefit on skin fibrosis assessed using the mRSS or health-related quality of life measured using the SGRQ was observed in patients treated with nintedanib versus placebo in the subgroups by use of mycophenolate at baseline.

Mycophenolate suppresses the proliferation of T lymphocytes and B lymphocytes and induces apoptosis of activated T lymphocytes,[21] whereas nintedanib has been found to have a number of antifibrotic, anti-inflammatory, and vascular remodelling effects in preclinical models of systemic sclerosis and SSc-ILD.[12–14] The numerical reduction in the rate of decline in FVC provided by nintedanib in participants taking mycophenolate at baseline suggests that combining immunosuppression with nintedanib might provide additional benefits in reducing the progression of interstitial lung disease. This hypothesis is supported by the finding that among patients taking mycophenolate at baseline, a smaller proportion in the nintedanib group than in the placebo group had a decline in FVC of at least 3·3% predicted, which has been estimated to be the minimum clinically important difference for worsening in FVC.[20] Furthermore, the annual rate of decline in FVC in participants taking mycophenolate at baseline who were treated with nintedanib (40·2 mL per year [SE 19·8]) was close to the annual rate of decline in FVC observed in healthy adults).[22]

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 per year (SE 19·0), 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 methods, we cannot draw any conclusions on the effect of mycophenolate on lung function because patients were not randomly assigned by use of mycophenolate. Notably, we found differences at baseline between the subgroups by mycophenolate use, including a lower FVC in the mycophenolate users than in those not using mycophenolate. Additionally, patients using mycophenolate at baseline were only eligible to enter the trial if they had taken a stable dose of mycophenolate for at least 6 months before randomisation. Therefore, the participants who were taking mycophenolate at baseline were not new mycophenolate users, but rather a selected population who were tolerant to mycophenolate and potentially more likely to be responders to mycophenolate. Assessing the benefits of initial combination therapy versus individual components or a sequential approach to treatment was not within the scope of this trial, nor was comparing the benefits of mycophenolate alone versus nintedanib alone. Further limitations of our analyses include the paucity of data characterising the mycophenolate users in terms of their duration of mycophenolate use before the trial, the dose of mycophenolate used, or their FVC trajectory before the trial, and that the trial was not powered for subgroup analyses. Thus, our findings should be interpreted with caution. Nonetheless, these data are the best available evidence on which to base clinical decisions around the use of the combination of mycophenolate and nintedanib in patients with SSc-ILD.

Both mycophenolate[23] and nintedanib[24] are associated with gastrointestinal adverse events, and systemic sclerosis itself is commonly associated with gastrointestinal problems.[25] Mycophenolate is also associated with an increased risk of infection.[23] Importantly, with the caveat that this population had been tolerating mycophenolate for at least 6 months before entering the trial, the combination of nintedanib plus mycophenolate appeared to have acceptable tolerability. In the nintedanib group, the proportion of patients with diarrhoea was similar between those who were and were not taking

mycophenolate at baseline. Upper respiratory tract infections were more common among patients taking mycophenolate at baseline than those who were not, but were not increased with nintedanib compared with placebo. Premature discontinuations due to adverse events were less common among patients taking mycophenolate at baseline but were more frequent with nintedanib than with placebo in both subgroups.

In summary, in patients with SSc-ILD, nintedanib reduced the progression of interstitial lung disease both in patients who were using mycophenolate at baseline and in those who were not, 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, EC-B, MGi, SS, and TMM contributed to the design of the SENSCIS trial. KBH, OD, MK, YA, AB, CPD, JHWD, AMH-V, DK, MDM, MCV, 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.

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Data sharing

Data sharing requests will be considered from research groups that submit a research proposal form and include a statistician on the research team. Data will be shared via a secure data access system. Further information on data sharing is provided in the appendix (p 8).

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