Extent of fibrosis and lung function decline in patients with systemic sclerosis and interstitial lung disease: data from the SENSCIS trial

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Key messages:

- A greater extent of fibrotic SSc-ILD was weakly associated with FVC decline over 52 weeks.
- A benefit from nintedanib appeared to exist irrespective of patients' extent of fibrotic SSc-ILD.

Abstract

Objective: To assess associations between the extent of fibrotic interstitial lung disease (ILD) and forced vital capacity (FVC) at baseline and change in FVC over 52 weeks in patients with systemic sclerosis-associated ILD (SSc-ILD) in the SENSCIS trial.

Methods: We used generalised additive models, which involve few assumptions and allow for interaction between non-linear effects, to assess associations between the extent of fibrotic ILD on high-resolution computed tomography (HRCT), and the interplay of extent of fibrotic ILD on HRCT and FVC % predicted, at baseline and FVC decline over 52 weeks.

Results: In the placebo group (n=288), there was weak evidence of a modest association between a greater extent of fibrotic ILD at baseline and a greater decline in FVC % predicted at week 52 (r: -0.09 [95% CI -0.2, 0.03]). Higher values of both the extent of fibrotic ILD and FVC % predicted at baseline tended to be associated with greater decline in FVC % predicted at week 52. In the nintedanib group (n=288), there was no evidence of an association between the extent of fibrotic ILD at baseline and decline in FVC % predicted at week 52 (r: 0.01 [95% CI: -0.11, 0.12]) or between the interplay of extent of fibrotic ILD and FVC % predicted at baseline and decline in FVC % predicted at week 52.

Conclusion: Data from the SENSCIS trial suggest that patients with SSc-ILD are at risk of ILD progression and benefit from nintedanib largely irrespective of their extent of fibrotic ILD at baseline.

Trial registration: ClinicalTrials.gov (NCT02597933).

Keywords: autoimmune diseases, pulmonary fibrosis, vital capacity.

Introduction

Systemic sclerosis (SSc) is a rare and heterogeneous autoimmune disease characterised by microvascular damage and progressive fibrosis of the skin and internal organs [1]. Interstitial lung disease (ILD) is the leading cause of death in subjects with SSc [2]. Patients with SSc-ILD who have fibrotic ILD of any extent on high-resolution computed tomography (HRCT) have an increased risk of mortality compared to those with no fibrotic ILD [3]. Further, a number of studies have suggested that a greater extent of fibrotic SSc-ILD on HRCT is associated with an increased risk of mortality [3-6]. Lower forced vital capacity (FVC) at baseline [3,4,7] or a decline in FVC [3,8,9] have also been associated with an increased risk of mortality in patients with SSc-ILD. These observations may not be independent, as a greater extent of fibrotic ILD on HRCT is associated with lower FVC [4,8,10].

In the randomised placebo-controlled SENSCIS trial in subjects with SSc-ILD, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by 44% [11] and reduced the proportions of subjects with a decline in FVC of >5% to ≤10% predicted or >10% to ≤15% predicted over 52 weeks [12]. Various approaches have been used to measure the extent of fibrotic SSc-ILD on HRCT and to evaluate the association between the extent of fibrotic SSc-ILD and FVC at baseline and outcomes. In these analyses, we used a flexible regression modeling approach, which allowed for interaction between potentially non-linear effects, to assess associations between the extent of fibrotic ILD on HRCT and FVC % predicted at baseline and change in FVC over 52 weeks in the SENSCIS trial.

Patients and methods

Trial design

The design of the SENSCIS trial (NCT02597933) has been published and the protocol is publicly available [11]. Briefly, subjects had SSc-ILD with onset of first non-Raynaud symptom in the prior ≤7 years, FVC ≥40% predicted, diffusion capacity of the lung for carbon monoxide (DLco) 30–89% predicted, and fibrotic ILD ≥10% extent on an HRCT scan taken in the last ≤12 months, confirmed by central assessment by an expert radiologist. A recent decline in FVC was not an inclusion criterion. The extent of fibrotic ILD (reticular abnormalities, honeycombing, fibrotic ground glass opacities) was assessed visually in the whole lung to the nearest 5%. Subjects on prednisone ≤10 mg/day (or equivalent) and/or stable therapy with mycophenolate or methotrexate were allowed to participate. Subjects were randomised to receive nintedanib or placebo, stratified by the presence of anti-topoisomerase I antibody (ATA), until the last subject had reached week 52 but for ≤100 weeks. Subjects who discontinued treatment prematurely were asked to attend visits as originally planned. The trial was conducted in accordance with the trial protocol, the principles of the Declaration of Helsinki, and the International Council for Harmonisation Guidelines for Good Clinical Practice. The trial was approved by an independent ethics committee or institutional review board at every site. The participating sites are listed in [11]. All subjects provided written informed consent.

Analyses

These *post-hoc* analyses were conducted in subjects who received ≥1 dose of trial medication. To explore associations between continuous variables, we used generalised additive models, a class of flexible regression models that allows consideration of potentially non-linear ("spline") effects of predictor variables and, for change in FVC, also their interactions. We assessed the association between the extent of fibrotic ILD at baseline and decline in FVC over 52 weeks, based on the absolute change from baseline in FVC % predicted and the rate of decline in FVC (mL/year). We assessed the association between the interaction of the extent of fibrotic ILD and FVC % predicted at baseline and FVC decline over 52 weeks, measured as the absolute change from baseline in FVC % predicted, absolute change from baseline in FVC (mL), and rate of decline in FVC (mL/year). We also assessed the association between the extent of fibrotic ILD and FVC % predicted at baseline. Linear associations were evaluated using Pearson correlation coefficients. In analyses of change from baseline in FVC (but not of the rate of decline in FVC), missing FVC values were imputed using a worst observation carried forward approach. These analyses were performed in the nintedanib and placebo groups overall and in subgroups by use of mycophenolate at baseline. Generalised additive models were fit in R, version 1.8-28, using the package "mgvc" package [https://cran.r-project.org/src/contrib/Archive/mgcv/]. The univariate and bivariate (interaction) smoothing terms were penalised thin plate regression splines. The smoothing parameters were estimated using the restricted maximum likelihood (REML) estimation method.

As a supplementary analysis, we assessed outcomes in subgroups based on thresholds of an extent of fibrotic ILD of 40% and an FVC of 70% predicted at baseline in the overall population. In these subgroups, we analysed the rate of decline in FVC (mL/year) over 52 weeks; the proportions of subjects who met proposed thresholds for minimal clinically important differences for improved, stable, or worsened FVC based on data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36 (absolute increase ≥3.0% predicted, absolute increase <3.0% predicted or decrease <3.3% predicted, absolute decrease ≥3.3% predicted) [13] at week 52; and time to absolute decline in FVC ≥10% predicted, or absolute decline in FVC ≥5% to <10% predicted with an absolute decline in DLco ≥15% predicted, or death at week 52. Statistical analyses of these outcomes are described in the Supplementary Material.

Results

Subjects

A total of 576 subjects received ≥1 dose of trial medication (288 nintedanib, 288 placebo). Their baseline characteristics have been described [11]. Briefly, in the nintedanib and placebo groups, respectively, the mean (SD) extent of fibrotic ILD (%) was 36.8 (21.8) and 35.2 (20.7), mean (SD) FVC was 2459 (736) and 2541 (816) mL, mean (SD) FVC % predicted was 72.4 (16.8) and 72.7 (16.6), and 48.3% and 48.6% of subjects were taking mycophenolate.

Association between extent of fibrotic ILD at baseline and decline in FVC over 52 weeks

In the placebo group, there was weak evidence of a modest inverse association between the extent of fibrotic ILD at baseline and the decline in FVC % predicted at week 52 in the overall population (Figure 1) and in subgroups of subjects who were taking and not taking mycophenolate at baseline (Figure 2). There was no association between the extent of fibrotic ILD at baseline and the rate of decline in FVC (mL/year) over 52 weeks (Supplementary Figures 1 and 2). In the nintedanib group, there was no evidence of an association between the extent of fibrotic ILD on HRCT at baseline and decline in FVC % predicted at week 52 in the overall population (Figure 1) or in subgroups of subjects based on use of mycophenolate at baseline (Figure 2). Similarly, there was no evidence of an association between the extent of fibrotic ILD at baseline and the rate of decline in FVC (mL/year) over 52 weeks (Supplementary Figures 1 and 2).

Interaction of extent of fibrotic ILD and FVC % predicted at baseline and decline in FVC over 52 weeks

In the placebo group, higher values of both the extent of fibrotic ILD and FVC % predicted at baseline tended to be associated with a greater decline in FVC % predicted (Figure 3), greater decline in FVC (mL) (Supplementary Figure 3) and greater rate of decline in FVC (mL/year) over 52 weeks (Supplementary Figure 4). However, these areas were sparsely populated with subjects and none of the bivariate smooth terms in the models reached statistical significance (all p-values >0.15). The association between the interplay of the extent of fibrotic ILD and FVC % predicted at baseline and the decline in FVC % predicted over 52 weeks in the

placebo group was more pronounced in subjects taking than not taking mycophenolate at baseline (Figure 4). Similar patterns were observed in subjects who were and were not taking mycophenolate at baseline (Supplementary Figures 5 and 6).

In the nintedanib group, there was no evidence of an association between the interplay of the extent of fibrotic ILD and FVC % predicted at baseline and decline in FVC % predicted at week 52 (Figure 3), decline in FVC (mL) at week 52 (Supplementary Figure 3) or rate of decline in FVC (mL/year) over 52 weeks (Supplementary Figure 4). Similar results were observed in subgroups by use of mycophenolate at baseline (Figure 4; Supplementary Figures 5 and 6).

Association between extent of fibrotic ILD and FVC at baseline

A greater extent of fibrotic ILD at baseline was weakly associated with a lower FVC % predicted at baseline both in the placebo group (r: -0.25 [95% CI: -0.35, -0.14) and in the nintedanib group (r: -0.18 [95% CI: -0.29, -0.07]) (Figure 5). An extent of fibrotic ILD of 40% was associated with an FVC of 70% predicted.

Subgroup analyses based on extent of fibrotic ILD and FVC % predicted at baseline

Based on the above finding, we analysed outcomes in subgroups with an extent of fibrotic ILD on HRCT ≥10 to ≤30% versus an extent of fibrotic ILD on HRCT >40% or an extent of fibrotic ILD on HRCT >30% to ≤40% with FVC <70% predicted. In the placebo group, compared with subjects with an extent of fibrotic ILD ≥10 to ≤30%, the rate of decline in FVC (mL/year) over 52 weeks was numerically greater in

subjects with an extent of fibrotic ILD >40% or an extent of fibrotic ILD >30% to ≤40% with FVC <70% predicted (Supplementary Figure 7). The proportion of subjects with a decrease in FVC ≥3.3% predicted over 52 weeks was similar between these subgroups (Supplementary Table). The effect of nintedanib versus placebo on reducing the rate of decline in FVC (mL/year) was numerically more pronounced in subjects with an extent of fibrotic ILD >40% or an extent of fibrotic ILD >30% to ≤40% with FVC <70% predicted, but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect between these subgroups (p=0.40) (Supplementary Figure 7). The proportion of subjects with a decrease in FVC ≥3.3% predicted over 52 weeks was lower in subjects treated with nintedanib than placebo in both subgroups (Supplementary Table). The proportion of subjects with an absolute decline in FVC ≥10% predicted, or an absolute decline in FVC ≥5% to <10% predicted with absolute decline in DLco ≥15% predicted, or who died over 52 weeks was similar between placebo-treated subjects with an extent of fibrotic ILD ≥10 to ≤30% and those with an extent of fibrotic ILD >40% or extent of fibrotic ILD >30% to ≤40% with FVC <70% predicted, and lower in subjects treated with nintedanib than placebo in both subgroups (Supplementary Table).

Discussion

In patients with SSc-ILD, a greater extent of fibrotic ILD on HRCT, and a lower FVC at baseline, have been associated with a higher rate of ILD progression and mortality [3-7,14,15]. These relationships may be considered in terms of thresholds or by considering the extent of fibrotic ILD and FVC as continuous variables. While cut-offs are useful for clinical decision-making, in reality associations are likely to be gradual and not necessarily linear. We used a flexible regression modeling approach to

assess associations between the extent of fibrotic ILD and FVC % predicted at baseline and change in FVC over 52 weeks in the SENSCIS trial. This approach offers advantages over linear regression models, as non-linear effects and interactions are considered, giving greater flexibility and involving fewer assumptions [16]. Among subjects who received placebo, we found only weak evidence of a modest association between a greater extent of fibrotic ILD at baseline and a greater decline in FVC over the following 52 weeks. In patients taking both nintedanib and mycophenolate, there was weak evidence of a very modest association between a greater extent of fibrotic ILD on HRCT at baseline and a lower decline in FVC over the following 52 weeks. Analyses of data from Scleroderma Lung Study I based on linear mixed effects modelling [14] and correlation analyses [15], and a proportional hazards analysis of data from the Goh et al study [4], found stronger associations between the extent of fibrotic SSc-ILD at baseline and the rate of decline in FVC. The differences between the findings of these studies and those of our overall analyses of data from the SENSCIS trial may relate to differences in the patient populations evaluated or to the medications that they were taking, as well as to differences in study design and statistical methodologies. For example, the Goh et al study [4] enrolled patients with any extent of ILD on HRCT, while patients in the SENSCIS trial had fibrotic ILD of ≥10% extent on HRCT.

Our results suggest that a higher FVC % predicted at baseline was associated with a greater absolute decline in FVC % predicted during the SENSCIS trial. This may reflect that patients who had a higher FVC at baseline had a greater respiratory reserve to lose over the following 52 weeks. Consistent with this, a recent analysis of 826 patients with SSc-ILD in the EUSTAR database found that a greater FVC %

predicted at baseline was associated with a higher risk of a decline in FVC >10 to 20% predicted over the next 12 months [17]. However, linear modelling of data from Scleroderma Lung Study I found no association between FVC % predicted at baseline and decline in FVC % predicted over the next 12 months [14]. As observed in previous studies [4,8,10,18], in our study, a greater extent of fibrotic ILD was associated with lower FVC % predicted at baseline, but the correlation was weak.

Clinicians may be more likely to initiate treatment in patients with SSc-ILD who have a greater extent of fibrotic ILD and/or a lower FVC % predicted [19-21] based on a belief that these patients' ILD is more likely to progress. A *post-hoc* analysis of data from Scleroderma Lung Study I suggested that patients with more severe reticular changes on HRCT may have a greater response to cyclophosphamide [22]. However, *post-hoc* analyses of data from the subgroup of patients with early diffuse cutaneous SSc and ILD in the focuSSced trial indicated that the effect of tocilizumab on FVC did not vary by quantitative ILD or lung fibrosis scores at baseline [18]. In our analyses, we found only small, non-significant differences in the effect of nintedanib on the rate of decline in FVC between subjects with differing extents of fibrotic ILD or FVC % predicted at baseline. These findings add to previous analyses of the SENSCIS trial that showed no heterogeneity in the effect of nintedanib on the rate of FVC decline across subgroups based on FVC thresholds of 60%, 70%, 80% and 90% predicted at baseline [23-25]. In the nintedanib group, the findings of our current analyses were similar in subjects who were and were not taking mycophenolate at baseline, consistent with the pre-specified analysis that showed a consistent effect of nintedanib on the rate of FVC decline between these subgroups [26]. Taken together, these findings suggest that baseline characteristics alone, including the

extent of fibrotic ILD on HRCT, cannot be used to inform which patients with SSc-ILD should be given nintedanib, as its relative effect is similar across the spectrum of disease severity. We acknowledge that the same degree of ILD progression would likely have more of an impact on functional limitations in patients with more severe disease. However, an argument can also be made for targeting fibrosis in patients with early ILD to slow irreversible loss of lung function in those patients and so improve outcomes, including survival. This argument is strengthened by the unpredictable clinical course of SSc-ILD, which makes it difficult to predict in which patients ILD will remain “mild” [3,17]. In clinical practice, therapeutic decisions need to be made based on more information than markers of disease severity at a given time-point, including evidence of and risk factors for progression, other manifestations of SSc or comorbidities, and patient preferences [19, 21].

Strengths of our analyses include the large sample size, flexible modeling approach, assessment of the extent of fibrotic ILD in the whole lung, based on central review of HRCT scans, and robust measurement of FVC. When interpreting our analyses, it should be borne in mind that the extent of fibrotic ILD on HRCT in the SENSCIS trial was determined using a different methodology to that used in studies such as the Goh et al study [4] in which the extent of fibrotic ILD was estimated visually to the nearest 5% in five sections and the overall extent computed as the mean of these five scores. This methodology based on assessment of five sections, not including the bases of the lungs, provides a lower estimate for the total extent of fibrotic ILD than the methodology based on assessment of the whole lung that was used in the SENSCIS trial. This is reflected in the observation that an FVC of 70% predicted at baseline reflected an extent of fibrotic ILD of 40% in our analyses but an extent of

fibrotic ILD of 20% in the Goh et al study [4]. Differences in methodology used to quantify fibrotic ILD on HRCT need to be borne in mind in the comparison of subgroup analyses based on data from different studies. In general, comparisons between the current study and the Goh et al study [4] should be approached with caution, given the differences between the aims, methodologies, durations, and patient populations in these studies.

Limitations of our analyses include that the SENSCIS trial was not designed to evaluate associations between the extent of fibrotic ILD on HRCT and FVC % predicted at baseline and change in FVC; that a follow-up period of 52 weeks may be too short to detect such associations; and that our analyses were conducted *post-hoc*, so our findings should be considered exploratory. Even under the standardised conditions of a clinical trial, measurements of the extent of fibrotic ILD on HRCT and of FVC are subject to error, which may attenuate associations. The use of a single expert radiologist to assess the extent of fibrotic ILD on HRCT meant that inter-reader variability could not be assessed. The exclusion of patients with an FVC <40% predicted or a DLco <30% predicted from the trial may have influenced our findings. The generalizability of our findings beyond patients who met the inclusion criteria for the SENSCIS trial is unknown. Only 19 deaths occurred over the entire SENSCIS trial so we could not evaluate the association between the extent of fibrotic ILD or FVC at baseline and mortality.

In conclusion, using contemporary methodology involving few assumptions, we found weak evidence of a modest inverse association between the extent of fibrotic ILD at baseline and decline in FVC over 52 weeks among patients with SSc-ILD who

received placebo in the SENSCIS trial. There were small numerical differences in the effect of nintedanib on slowing the rate of decline in FVC among patients who had differing extents of fibrotic ILD or FVC % predicted at baseline assessed as continuous variables. These findings suggest that patients with SSc-ILD are at risk of progression and benefit from treatment with nintedanib largely irrespective of the severity of their ILD at baseline.

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Data availability statement: Data are available upon reasonable request (see Supplementary Material).

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Figure 1. Associations between extent of fibrotic ILD on HRCT at baseline and change in FVC % predicted at week 52; dashed lines indicate 95% confidence intervals.

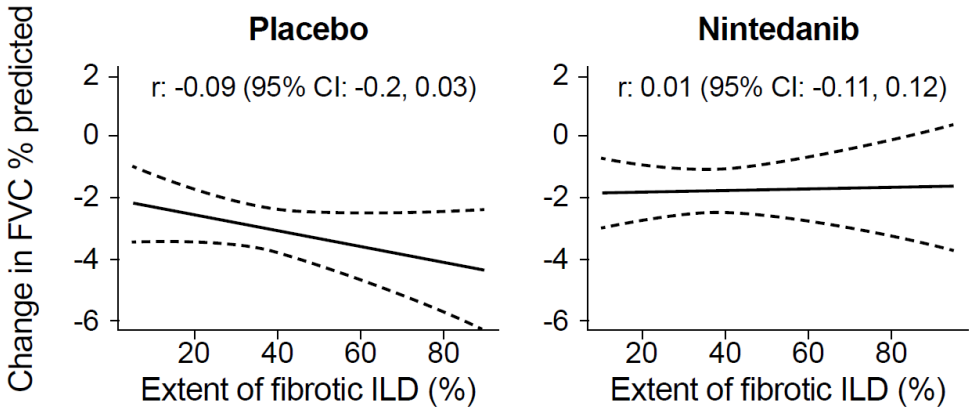
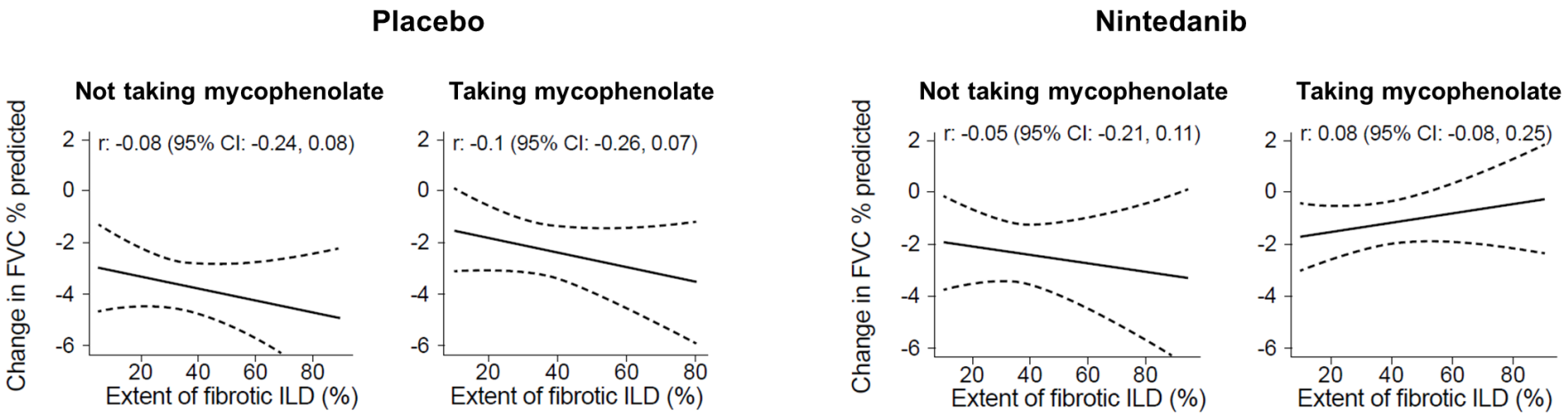


Figure 2. Associations between extent of fibrotic ILD on HRCT at baseline and change in FVC % predicted at week 52 in subgroups by mycophenolate use at baseline; dashed lines indicate 95% confidence intervals.



Subjects taking mycophenolate had to have taken a stable dose for ≥6 months before randomization.

Figure 3. Contour plots of change in FVC % predicted at week 52 by extent of fibrotic ILD on HRCT and FVC % predicted at baseline; darker shading indicates greater decline in FVC % predicted at week 52.

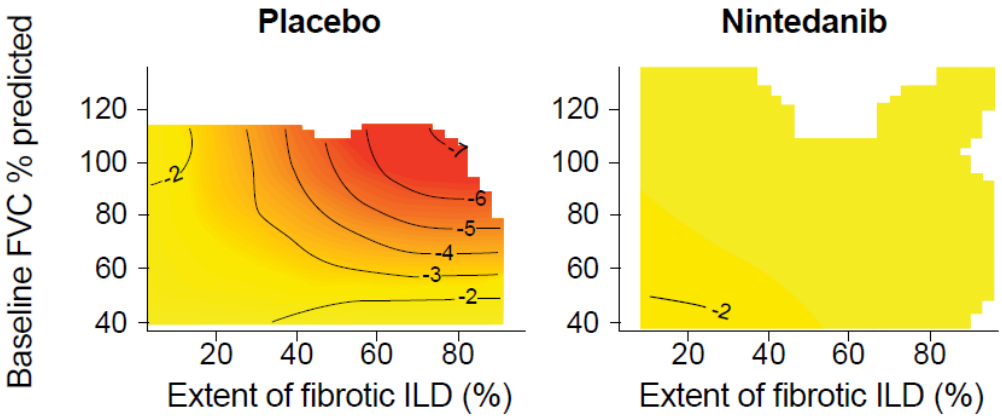
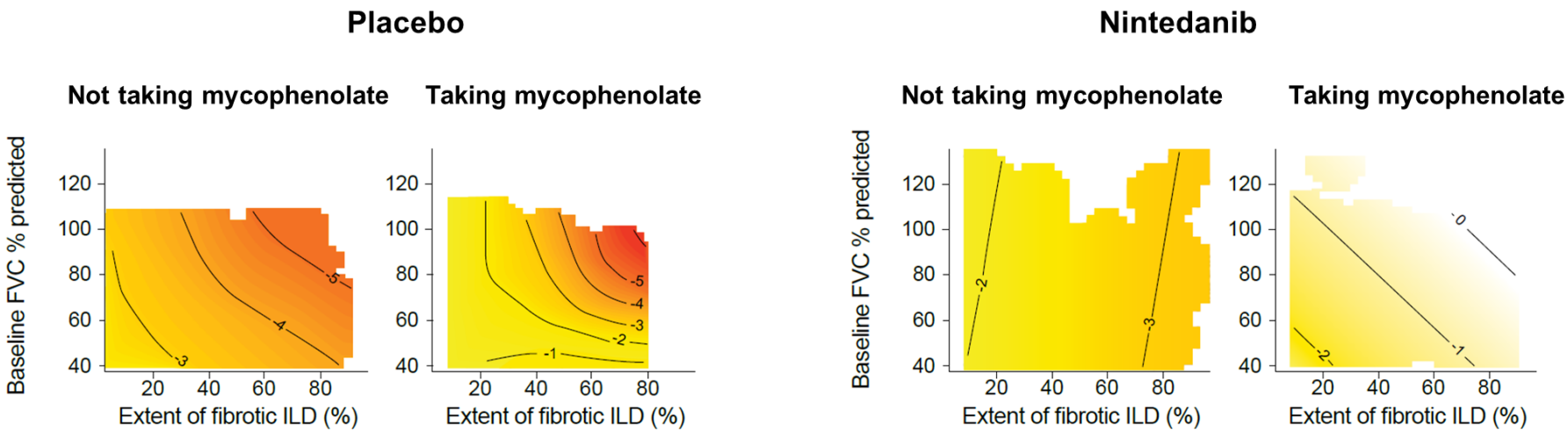
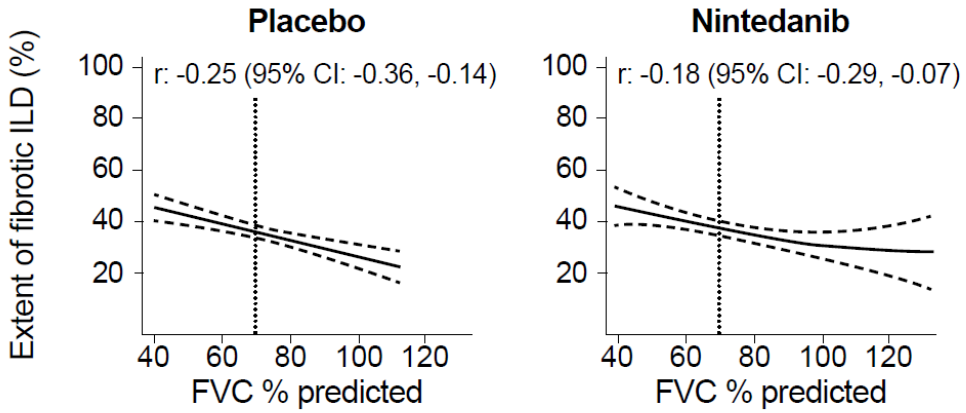


Figure 4. Contour plots of change in FVC % predicted at week 52 by extent of fibrotic ILD on HRCT and FVC % predicted at baseline in subgroups by mycophenolate use at baseline; darker shading indicates greater decline in FVC % predicted at week 52.



Subjects taking mycophenolate had to have taken a stable dose for ≥6 months before randomization.

Figure 5. Associations between extent of fibrotic ILD and FVC % predicted at baseline.



SUPPLEMENTARY MATERIAL

Statistical analysis of outcomes in subgroups with an extent of fibrotic interstitial lung disease (ILD) on high-resolution computed tomography (HRCT) ≥10 to ≤30% versus an extent of fibrotic ILD on HRCT >40% or an extent of fibrotic ILD on HRCT >30% to ≤40% with forced vital capacity (FVC) <70% predicted at baseline

The rate of decline in FVC (mL/year) over 52 weeks in these subgroups was analysed using a random coefficient regression model (with random slopes and intercepts) with fixed categorical effects of anti-topoisomerase I antibody (ATA) status and sex, fixed continuous effects of baseline FVC (mL), age, and height and including baseline−by−time, treatment−by−subgroup and treatment−by−subgroup−by−time interaction terms.

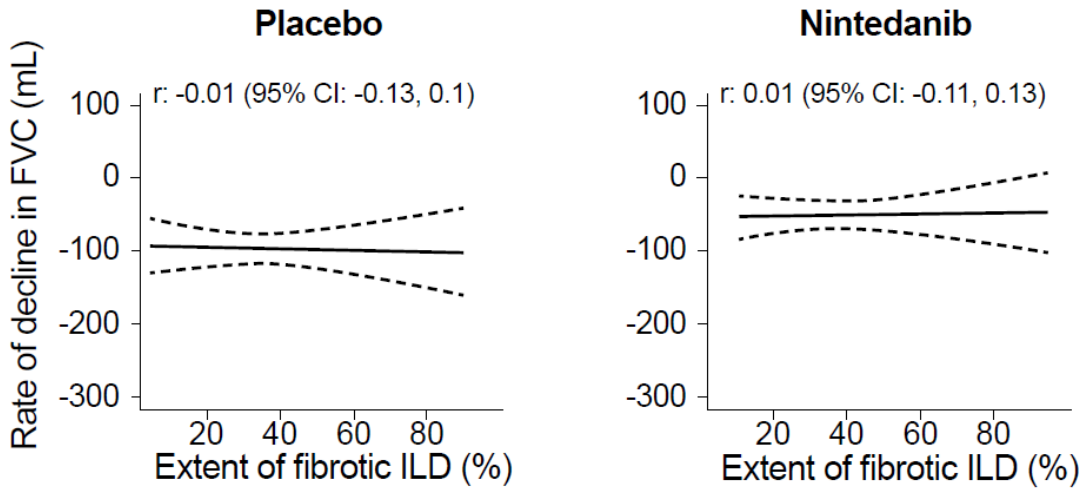
The proportions of subjects with an absolute increase in FVC ≥3.0% predicted, absolute increase in FVC <3.0% predicted or decrease in FVC <3.3% predicted, and absolute decrease in FVC ≥3.3% predicted at week 52 were compared between subgroups using a logistic regression model including terms for treatment, ATA status, subgroup and treatment−by−subgroup interaction. Odds ratios were estimated for the effect of treatment within each subgroup. Missing values were imputed using a worst value carried forward approach.

The time to absolute decline in FVC ≥10% predicted, or absolute decline in FVC ≥5% to <10% predicted with an absolute decline in diffusing capacity of the lungs for carbon monoxide (DLco) ≥15% predicted, or death at week 52 was analysed using a Cox proportional hazards model stratified by ATA status with terms for treatment,

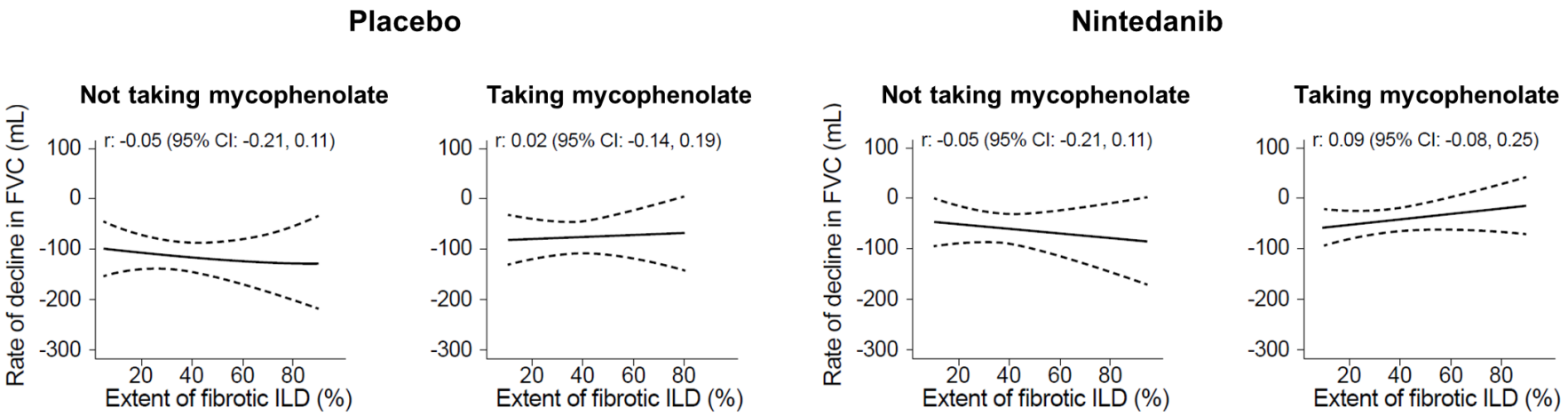
subgroup and treatment-by-subgroup interaction. Missing values were imputed using a worst value carried forward approach.

For all subgroup analyses, an interaction test was applied to assess potential heterogeneity in the effect of nintedanib between the subgroups, with no adjustment for multiple testing.

Supplementary Figure 1. Associations between extent of fibrotic ILD on HRCT at baseline and rate of decline in FVC (mL/year) over 52 weeks; dashed lines indicate 95% confidence intervals.

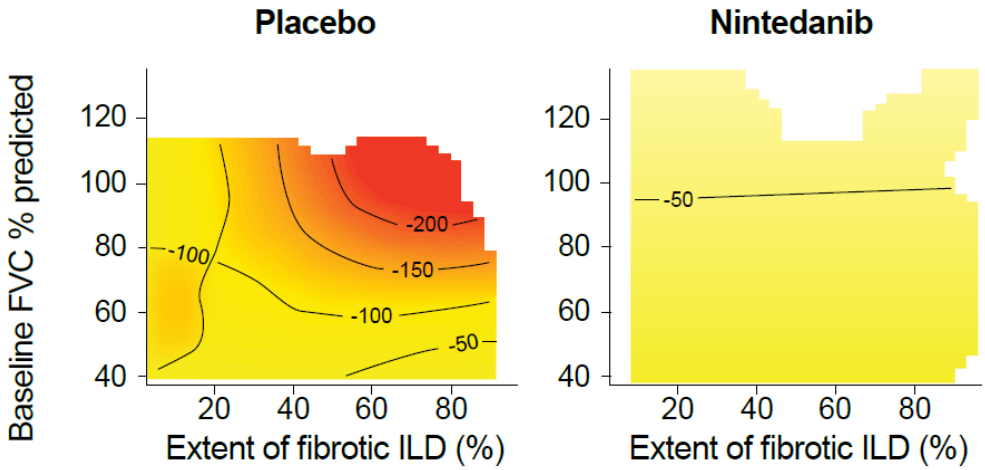


Supplementary Figure 2. Associations between extent of fibrotic ILD on HRCT at baseline and rate of decline in FVC (mL/year) over 52 weeks in subgroups by mycophenolate use at baseline; dashed lines indicate 95% confidence intervals.

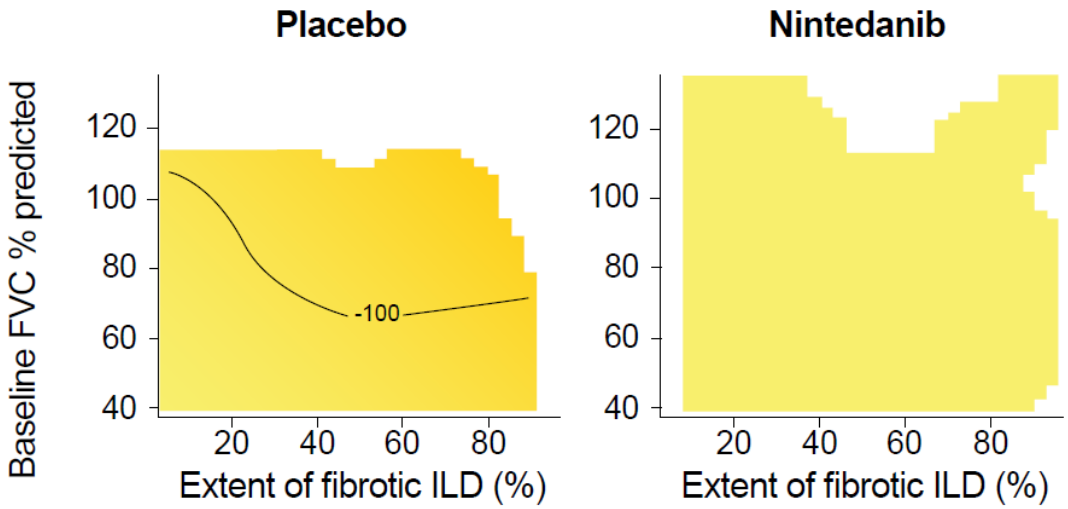


Subjects taking mycophenolate had to have taken a stable dose for ≥6 months before randomisation.

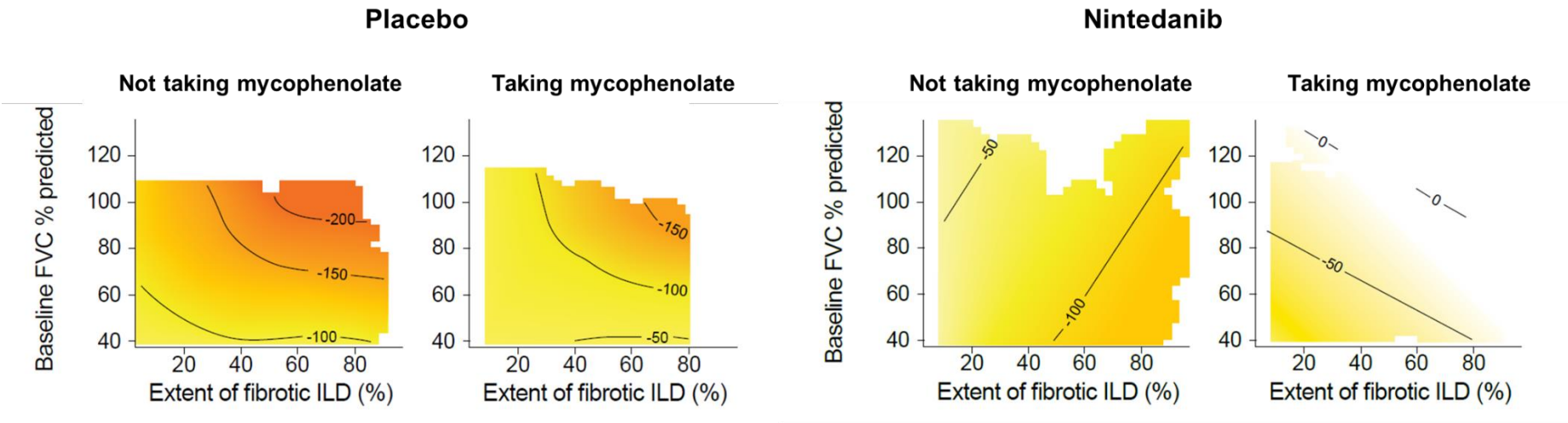
Supplementary Figure 3. Contour plots of change in FVC (mL) at week 52 by extent of fibrotic ILD on HRCT and FVC % predicted at baseline; darker shading indicates greater decline in FVC (mL) at week 52.



Supplementary Figure 4. Contour plots of rate of decline in FVC (mL/year) over 52 weeks by extent of fibrotic ILD on HRCT and FVC % predicted at baseline; darker shading indicates greater rate of decline in FVC.

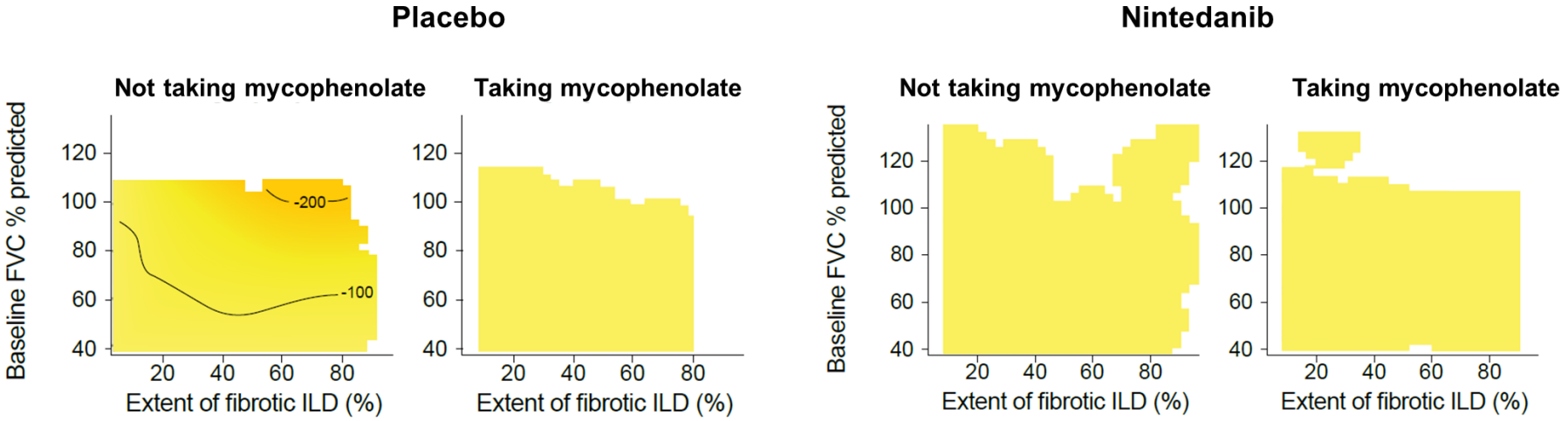


Supplementary Figure 5. Contour plots of change in FVC (mL) at week 52 by extent of fibrotic ILD on HRCT and FVC % predicted at baseline in subgroups by mycophenolate use at baseline; darker shading indicates greater decline in FVC (mL) at week 52.



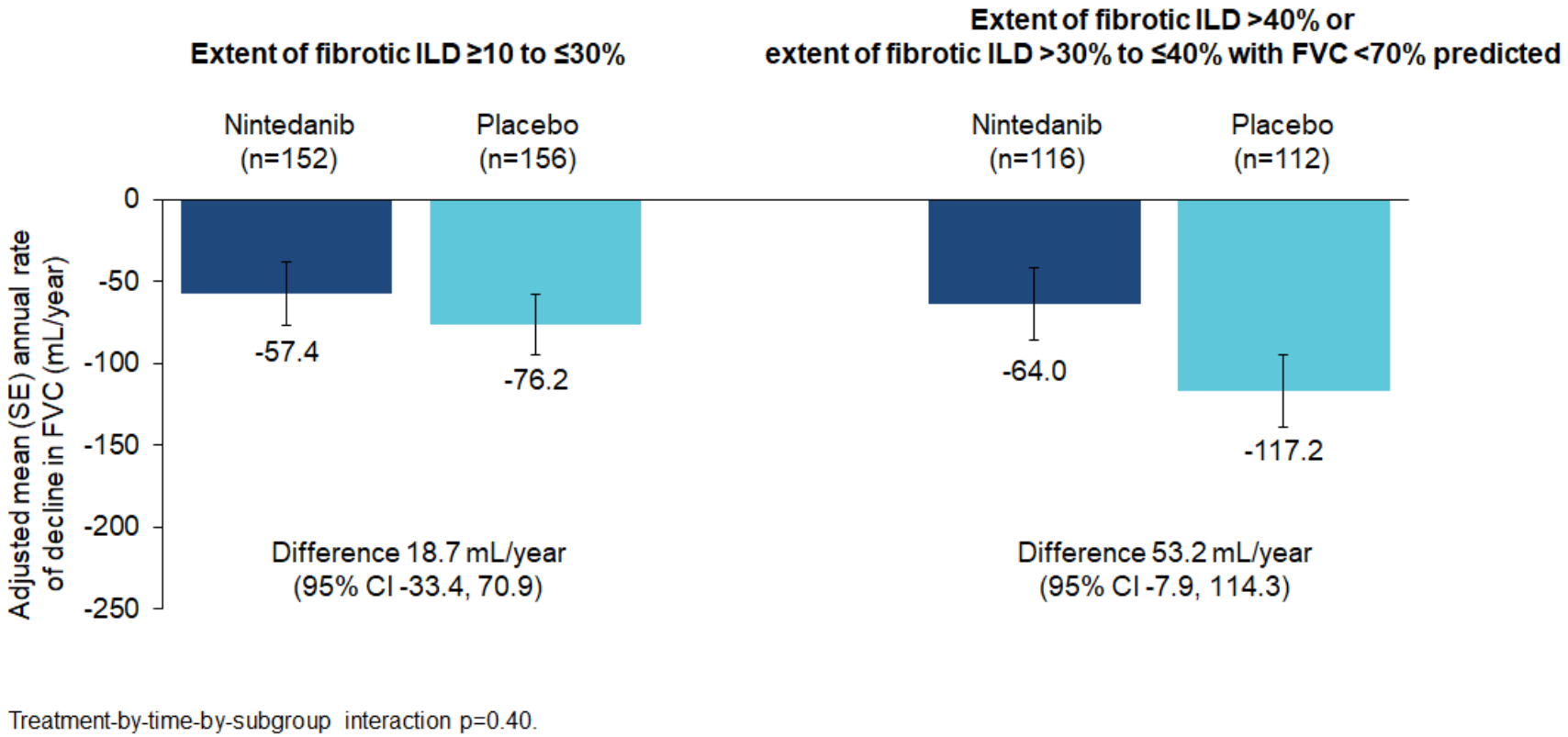
Subjects taking mycophenolate had to have taken a stable dose for ≥6 months before randomisation.

Supplementary Figure 6. Contour plots of rate of decline in FVC (mL/year) over 52 weeks by extent of fibrotic ILD on HRCT and FVC % predicted at baseline in subgroups by mycophenolate use at baseline; darker shading indicates greater rate of decline in FVC.



Subjects taking mycophenolate had to have taken a stable dose for ≥6 months before randomisation.

Supplementary Figure 7. Rate of decline in FVC (mL/year) over 52 weeks in subgroups by extent of fibrotic ILD on HRCT at baseline.



Treatment-by-time-by-subgroup interaction p=0.40.

Supplementary Table. Proportions of subjects with improvement, stability and worsening of FVC at week 52[a] and with absolute declines in FVC % predicted or death over 52 weeks in subgroups by extent of fibrotic ILD on HRCT at baseline.

	Extent of fibrotic ILD ≥10 to ≤30%		**Extent of fibrotic ILD >40% or >30% to ≤40% with FVC <70% predicted**	
	Nintedanib (n=152)	**Placebo (n=156)**	**Nintedanib (n=116)**	**Placebo (n=112)**
Increase in FVC ≥3.0% predicted[a]				
Number (%) of subjects	31 (20.4)	26 (16.7)	27 (23.3)	12 (10.7)
Odds ratio vs placebo (95% CI)	1.27 (0.71, 2.27)		2.55 (1.22, 5.33)	
Treatment-by-subgroup interaction	p=0.15			
Increase in FVC <3.0% predicted or decrease in FVC <3.3% predicted[a]				

Number (%) of subjects	64 (42.1)	62 (39.7)	52 (44.8)	50 (44.6)
Odds ratio vs placebo (95% CI)	1.10 (0.70, 1.74)		1.01 (0.60, 1.70)	
Treatment-by-subgroup interaction	p=0.80			
Decrease in FVC ≥3.3% predicted[a]				
Number (%) of subjects	57 (37.5)	68 (43.6)	37 (31.9)	50 (44.6)
Odds ratio vs placebo (95% CI)	0.78 (0.49, 1.23)		0.58 (0.34, 0.99)	
Treatment-by-subgroup interaction	p=0.40			
Absolute decline in FVC ≥10% predicted, or absolute decline in FVC ≥5% to <10% predicted with absolute decline in DLco ≥15% predicted, or death				
Number (%) of subjects	21 (13.8)	34 (21.8)	14 (12.0)[b]	27 (24.1)
Hazard ratio vs placebo (95% CI)	0.64 (0.37, 1.11)		0.45 (0.24, 0.87)	

Treatment-by-subgroup interaction	p=0.43

[a]Proposed thresholds for minimal clinically important differences for worsened, stable, or improved FVC based on estimates derived from Scleroderma Lung Studies I and II anchored to the health transition question from the Medical Outcomes Short Form-36 [1]. [b]Analysed in 117 subjects.

References

1. Kafaja S, Clements PJ, Wilhalme H, Tseng CH, Furst DE, Kim GH, et al. Reliability and minimal clinically important differences of forced vital capacity: results from the Scleroderma Lung Studies (SLS-I and SLS-II). Am J Respir Crit Care Med 2018;197:644–52.

Data availability statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent.

Researchers should use https://vivli.org to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.