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Stability or improvement in forced vital capacity with nintedanib in patients with IPF

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Take-home message

25% and 9% of nintedanib- and placebo-treated patients in INPULSIS had an improvement in FVC over 52 weeks

Abstract

In the Phase III INPULSIS® trials, nintedanib reduced the annual rate of decline in forced vital capacity (FVC) versus placebo in patients with IPF.

We conducted *post-hoc* analyses of the distribution of changes in FVC in the INPULSIS® trials and FVC changes in the open-label extension trial INPULSIS®-ON in subgroups of patients based on whether patients had shown an improvement/no decline in FVC in INPULSIS®. Analyses were descriptive.

Based on annual rate of change in FVC, 158 of 638 patients (24.8%) treated with nintedanib and 38 of 423 patients (9.0%) treated with placebo had an improvement or no decline in FVC in the INPULSIS® trials. In patients whose FVC improved or did not decline, median (interquartile range) improvements in FVC at week 52 were 76.5 (31–152) mL and 57.5 (31–103) mL in the nintedanib and placebo groups, respectively. Changes in FVC from baseline to week 48 of INPULSIS®-ON were similar in patients whose FVC improved or declined in the preceding INPULSIS® trial.

In the INPULSIS® trials, a greater proportion of patients with IPF treated with nintedanib than placebo had an improvement or no decline in FVC. Mechanisms underlying improvement in FVC in patients with IPF are unknown.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterised by progressive decline in lung function [1]. The clinical course of IPF is variable and unpredictable, with some patients declining rapidly, others progressing much more slowly, and some experiencing periods of relative stability punctuated by episodes of acute respiratory decline [2]. In the absence of therapies that can halt fibrosis, the goal of IPF treatment is to slow disease progression by reducing decline in lung function [3]. Decline in forced vital capacity (FVC) is recognised as a clinically relevant measure of disease progression in patients with IPF [4,5].

Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes fundamental to the pathogenesis of IPF, including the proliferation, migration and differentiation of fibroblasts, and the deposition of extracellular matrix (ECM), as well as having anti-inflammatory effects [6]. The efficacy and safety of 52 weeks' treatment with nintedanib 150 mg twice daily (bid) in patients with IPF were assessed in the two replicate Phase III INPULSIS® trials. In both trials, nintedanib significantly reduced the annual rate of decline in FVC compared with placebo (−113.6 vs −223.5 mL/year based on pooled data) [7]. A significantly smaller proportion of patients treated with nintedanib than placebo had a decline in FVC ≥5% predicted (47% versus 61%) or ≥10% predicted (30% versus 39%) from baseline to week 52 [8]. These thresholds of decline in FVC over 6–12 months have been shown to be predictive of mortality in patients with IPF [9,10]. Patients who completed the INPULSIS® trials were eligible to enter an open-label extension trial known as INPULSIS®-ON. Results from an interim analysis of data from INPULSIS®-ON suggest that the effect of nintedanib on reducing disease progression is maintained over long-term treatment [11].

In this manuscript, we present the results of a *post-hoc* analysis of the distribution of changes in FVC in the INPULSIS® trials and the average changes in FVC in patients whose FVC improved or did not decline (*i.e.,* who had no change or any increase in FVC) in the INPULSIS® trials. In addition, we describe the changes in FVC in INPULSIS®-ON in subgroups of patients based on whether or not patients had shown an improvement/no decline in FVC in the INPULSIS® trials.

Materials and methods

The design of the INPULSIS® trials has been described [7]. Briefly, patients with a diagnosis of IPF within the previous 5 years, FVC ≥50% predicted, forced expiratory volume in 1 second (FEV_1)/FVC ratio ≥0.7, and diffusing capacity of the lungs for carbon monoxide (DLco) 30–79% predicted were enrolled. In the absence of a surgical lung biopsy, patients had to have a high-

resolution computed tomography (HRCT) scan showing honeycombing and/or a combination of traction bronchiectasis and reticulation in the absence of atypical features of usual interstitial pneumonia (UIP). Patients were randomised (3:2) to receive nintedanib 150 mg bid or placebo for 52 weeks, with a follow-up visit 4 weeks later. Patients who completed the 52-week treatment period and follow-up visit were eligible to enter the open-label extension trial, INPULSIS®-ON. In both INPULSIS® and INPULSIS®-ON, dose reductions and treatment interruptions were permitted to manage adverse events. The protocols for both trials were approved by an ethics committee or institutional review board at every participating centre, and informed consent was obtained from all participants.

In the INPULSIS® trials, FVC was measured at baseline, at weeks 2, 4, 6, 12, 24, 36, and 52, and at the follow-up visit. Patients who prematurely discontinued trial medication were encouraged to attend all visits as originally planned. In INPULSIS®-ON, FVC was measured at baseline, at weeks 2, 4, 6, 12, 24, 36, 48 and then every 16 weeks. Spirometry was conducted using sponsor-provided machines and according to criteria provided by the American Thoracic Society and European Respiratory Society [12].

The annual rate of change in FVC in the INPULSIS® trials was analysed using a random coefficient regression model with fixed effects for sex, age, height and random effect of patient-specific intercept and time. All available FVC values from baseline to week 52 were used, including FVC measurements from the follow-up visit for patients who prematurely discontinued trial medication and did not complete study visits until week 52. The St George's Respiratory Questionnaire (SGRQ) [13] was used to assess health-related quality of life at baseline and at weeks 6, 12, 24, and 52 of the INPULSIS® trials.

Adverse events were documented according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Weight loss was recorded based on adverse events coded using the preferred term "weight decrease" in the MedDRA.

The following descriptive analyses were conducted *post-hoc* based on pooled data from both INPULSIS® trials: distribution of annual rate of change in FVC (mL/year) in the nintedanib and placebo groups in patients treated with ≥1 dose of study medication; change from baseline in FVC (mL) at week 52 in the nintedanib and placebo groups in patients whose FVC improved or did not decline based on the annual rate of change in patients treated with ≥1 dose of study medication; change from baseline in SGRQ total score at week 52 in the nintedanib and placebo groups in patients whose FVC improved or did not decline and in patients whose FVC declined based on the annual rate of change in FVC in patients treated with ≥1 dose of study medication; proportion of patients who had weight loss at week 52 in the nintedanib and placebo

groups in patients whose FVC improved or did not decline and in patients whose FVC declined based on the annual rate of change in FVC in patients treated with ≥1 dose of study medication; distributions of change from baseline in FVC in mL and % predicted at week 52 in the nintedanib and placebo groups in patients who had an FVC value at week 52; change from baseline in FVC in mL and % predicted at week 52 in the nintedanib and placebo groups in patients whose FVC improved or did not decline based on their FVC value at week 52. Analyses of change from baseline in FVC in mL and % predicted at week 52 in patients whose FVC improved or did not decline based on their FVC value at week 52 were repeated excluding patients whose FVC values improved by >800 mL (outliers) as these were likely to be false readings.

The following descriptive analyses were conducted *post-hoc* based on data from INPULSIS®-ON: change in FVC (mL) from baseline of INPULSIS®-ON at weeks 2, 4, 6, 12, 24, 36 and 48 of INPULSIS®-ON in subgroups of patients whose FVC improved or did not decline, or declined, in INPULSIS® based on the annual rate of change, in patients treated with ≥1 dose of study medication in INPULSIS®.

FVC % predicted was calculated using the following equations [14] for males: FVC predicted (L) = 5.76 x height (metres) − 0.026 x age (years) − 4.34, and for females: FVC predicted (L) = 4.43 x height (metres) − 0.026 x age (years) − 2.89.

Results

Patients

A total of 1061 patients were treated in the INPULSIS® trials (638 with nintedanib, 423 with placebo). Of 807 patients who completed an INPULSIS® trial, 734 (91%) patients were treated in INPULSIS®-ON, of whom 430 continued nintedanib (having taken nintedanib in INPULSIS®) and 304 initiated nintedanib (having taken placebo in INPULSIS®).

Improvement in FVC based on annual rate of change in FVC (mL/year) in INPULSIS®

The distributions of the annual rate of change in FVC (mL/year) in the nintedanib and placebo groups are presented in Figure 1 and Supplementary figure S1. Patients indicated by the bars on the left side of the graph are those whose FVC declined the most; patients indicated by the bars on the right side of the graph are those whose FVC improved the most. The distribution of the annual rate of change in FVC is further to the right in patients treated with nintedanib than placebo. Based on the annual rate of change in FVC (mL/year), 158 of 638 patients (24.8%) in the nintedanib group and 38 of 423 patients (9.0%) in the placebo group had an improvement or

no decline (no change) in FVC. In patients whose FVC improved or did not decline based on the annual rate of change, median (interquartile range) improvements in FVC at week 52 were 76.5 (31–152) mL in the nintedanib group and 57.5 (31–103) mL in the placebo group.

Baseline characteristics including age, sex, weight, FVC, or presence of honeycombing on HRCT were generally similar between patients whose FVC improved or did not decline in INPULSIS® and patients whose FVC declined based on the annual rate of change in FVC (Table 1; Supplementary figures S2–5).

Improvement in FVC based on change from baseline in FVC in INPULSIS®

In total, 864 (81.4%) of the treated patients had an FVC value at week 52 (519 treated with nintedanib, 345 with placebo). The distribution of changes in FVC (mL) in the nintedanib and placebo groups in patients with an FVC value at week 52 is presented in Supplementary figure S6. Based on change from baseline in FVC (mL) at week 52, 191 patients (36.8%) in the nintedanib group had an improvement or no decline in FVC (of whom 181 had an improvement) and 62 patients (18.0%) in the placebo group had an improvement or no decline in FVC (of whom 55 had an improvement). Three outliers in the placebo group had a change from baseline in FVC at week 52 of >800 mL (883 mL, 1267 mL, 1578 mL).

In patients whose FVC improved or did not decline based on change from baseline in FVC (mL), median (interquartile range) improvements in FVC at week 52 were 110 (47–227) mL in the nintedanib group and 105 (39–175) mL in the placebo group [or 98 (39–169) mL if the three outliers with increases in FVC >800 mL were excluded].

The distribution of mean changes in FVC % predicted in the nintedanib and placebo groups in patients with an FVC value at week 52 is presented in Supplementary figure S7. In patients whose FVC improved or did not decline based on change from baseline in FVC (mL), median (interquartile range) improvements in FVC % predicted at week 52 were 3.3 (1.6–6.7) % predicted in the nintedanib group and 3.2 (1.4–5.0) % predicted in the placebo group [or 3.0 (1.4–4.9) % predicted if the three outliers with increases >800 mL were excluded].

Changes in SGRQ

In patients whose FVC improved or did not decline based on the annual rate of change, mean (SD) change from baseline in SGRQ total score at week 52 was −1.9 (13.5) and −1.9 (17.6) in the nintedanib and placebo groups, respectively. In patients whose FVC declined based on the annual rate of change, mean (SD) change from baseline in SGRQ total score at week 52 was 4.9 (16.0) and 5.2 (15.4) in the nintedanib and placebo groups, respectively.

Weight loss

In patients whose FVC improved or did not decline based on the annual rate of change, 17 patients (10.8%) and 2 patients (5.3%) in the nintedanib and placebo groups, respectively, had weight loss at week 52. In patients whose FVC declined based on the annual rate of change, 45 patients (9.4%) and 13 patients (3.4%) in these groups, respectively, had weight loss at week 52.

INPULSIS®-ON

In patients treated with nintedanib in INPULSIS® whose FVC improved or did not decline in INPULSIS® based on the annual rate of change in FVC (n=158), mean (SD) change in FVC from baseline at week 48 of INPULSIS®-ON was −70 (246) mL (Table 2). In patients treated with nintedanib in INPULSIS® whose FVC declined in INPULSIS® based on the annual rate of change in FVC (n=480), mean (SD) change in FVC from baseline at week 48 of INPULSIS®-ON was −110 (231) mL.

In patients treated with placebo in INPULSIS® whose FVC improved or did not decline in INPULSIS® based on the annual rate of change in FVC (n=38), mean (SD) FVC change from baseline at week 48 of INPULSIS®-ON was −45 (226) mL. In patients treated with placebo in INPULSIS® whose FVC declined in INPULSIS® based on the annual rate of change in FVC (n=385), mean (SD) FVC change from baseline at week 48 of INPULSIS®-ON was −76 (246) mL.

Discussion

Based on pooled data on the annual rate of change in FVC in the two INPULSIS® trials, a greater proportion of patients treated with nintedanib than placebo had an improvement or no decline in FVC over 52 weeks of treatment (24.8% versus 9.0%). Among patients whose FVC improved or did not decline, the median improvement in FVC was approximately 77 mL in the nintedanib group and 58 mL in the placebo group. Although spirometric measurements are subject to a small degree of error [12], it is clear from the distribution of changes in FVC that in some patients, the improvements in FVC were larger than could be explained by errors in measurement.

None of the baseline characteristics that we studied was predictive of improvement in FVC over the course of the INPULSIS® trials. This finding is in line with previous subgroup analyses of the INPULSIS® trials showing that the treatment effect of nintedanib on FVC is

consistent across subgroups defined by baseline characteristics including FVC % predicted [15,16], DLco % predicted [17], diagnostic criteria (features of possible UIP with traction bronchiectasis on HRCT versus honeycombing on HRCT and/or confirmation of UIP by surgical lung biopsy) [18], presence/absence of honeycombing on HRCT [19] and presence/absence of emphysema [20]. IPF is a complex and heterogeneous disease that is known to have an unpredictable clinical course [2,21-23]. Thus it should perhaps not be surprising that these analyses did not identify baseline characteristics that were predictive of an improvement in FVC. Changes in FVC from baseline to week 48 of the extension trial INPULSIS®-ON were similar in patients whose FVC improved in the preceding INPULSIS® trial as in patients whose FVC declined in the preceding INPULSIS® trial. This is consistent with previous studies showing that decline in FVC is a poor predictor of future FVC decline, including an analysis of data from the INPULSIS® trials showing that change in FVC % predicted in the first 24 weeks did not predict FVC decline in the following 24 weeks [24]. It should be acknowledged, however, that studies showing that FVC decline is a poor predictor of FVC decline may be confounded by infrequent measurement and the occurrence of acute exacerbations. Studies in which FVC has been measured daily or weekly provide a more accurate picture of disease behaviour and have demonstrated a largely linear decline in FVC over 12 months in patients with IPF [25,26].

There is some evidence to suggest that the SGRQ total score is sensitive to detecting change in patients with IPF whose FVC % predicted declines or improves [27-30]. In our study, patients whose FVC improved or did not decline in INPULSIS® had a decrease (improvement) in SGRQ total score (−1.9 points in each treatment group) whereas patients whose FVC declined had an increase (worsening) in SGRQ total score (4.9 points in the nintedanib group and 5.2 points in the placebo group). The minimal clinically important difference of the SGRQ total score in patients with IPF has been estimated to be between 4 and 10 points [27,30], suggesting that the difference in change in SGRQ score between patients whose FVC improved and declined might reflect a clinically relevant difference in change in health-related quality of life in these groups of patients. Further analyses of data from the INPULSIS® trials have shown that stability/improvement in FVC over 52 weeks is associated with improvement in scores on other patient-reported outcomes, including the CASA-Q cough domains and EQ-5D VAS [31].

The observation that a minority of patients with IPF showed an improvement in FVC over the 52 weeks of the INPULSIS® trials challenges the concept that FVC can only decline in patients with IPF, although ultimately the disease will progress and lead to death in all patients. It should be noted that there was a mean decline in FVC in INPULSIS®-ON in the subgroup of patients whose FVC improved or did not decline in the preceding INPULSIS® trial. Treatment

with nintedanib increased the likelihood of a patient showing an improvement in FVC. The mechanism(s) by which nintedanib might lead to an improvement in FVC is unknown. Nintedanib has been shown to reduce the secretion of ECM and upregulate matrix metalloproteinases that degrade the ECM [6,32]. Thus in regions of the fibrotic lung that have not been decellularised and in which there is still turnover of extracellular matrix, *i.e*., both deposition and degradation, it may be hypothesised that nintedanib treatment leads to a net reduction in the excess of extracellular matrix, resulting in an improvement in lung function. Further, recently published data from a mouse model of pulmonary fibrosis showed that short-term nintedanib treatment not only reduced lung fibrosis and vascular proliferation, but essentially normalised the distorted microvascular architecture [33], suggesting that a restoration of alveolar structures may contribute to an improvement in lung function in some patients treated with nintedanib. Further research is needed to elucidate the mechanisms by which FVC might be improved in patients with IPF.

These analyses have some limitations. As *post-hoc* analyses, they should be regarded as exploratory. Not all patients had an FVC value at week 52. The INPULSIS®-ON trial lacked a placebo comparator and is subject to bias in the population who completed an INPULSIS® trial and so were eligible to participate.

In conclusion, in a *post-hoc* analysis of pooled data from the INPULSIS® trials, a greater proportion of patients with IPF treated with nintedanib than placebo had an improvement or no decline in FVC over 52 weeks. No baseline characteristics were identified that predicted an improvement in FVC. The mechanisms behind improvement in FVC in patients treated with nintedanib are unknown.

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Tables

Table 1. Baseline characteristics in INPULSIS® by annual rate of change in FVC in INPULSIS®

	Improvement or no decline in FVC		Decline in FVC	
	Nintedanib (n=158)	Placebo (n=38)	Nintedanib (n=480)	Placebo (n=385)
Age, years, mean (SD)	66.3 (7.9)	67.6 (8.2)	66.7 (8.2)	66.9 (7.9)
Male, n (%)	126 (79.7)	31 (81.6)	381 (79.4)	303 (78.7)
Race, n (%)				
White	99 (62.7)	24 (63.2)	261 (54.4)	224 (58.2)
Black	1 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)
Asian	38 (24.1)	11 (28.9)	156 (32.5)	117 (30.4)
Missing*	20 (12.7)	3 (7.9)	62 (12.9)	44 (11.4)
Former or current smoker, n (%)	130 (82.3)	28 (73.7)	334 (69.6)	273 (70.9)
Weight, kg, mean (SD)	82.6 (15.4)	83.9 (18.0)	78.1 (16.8)	78.1 (16.3)
Time since diagnosis of IPF, years, mean (SD)	1.6 (1.4)	1.5 (1.1)	1.7 (1.4)	1.6 (1.3)
FVC, mL, mean (SD)	2850 (782)	2949 (827)	2669 (744)	2706 (806)
FVC, % predicted, mean (SD)	81.6 (18.1)	84.4 (19.8)	79.1 (17.4)	78.8 (18.0)
DLco, % predicted, mean (SD)	47.5 (12.3)	50.7 (17.1)	47.4 (13.9)	46.6 (12.9)
Diagnostic subgroup, n (%)				
No honeycombing on HRCT and no biopsy	50 (31.7)	8 (21.1)	163 (34.0)	117 (30.4)
Honeycombing on HRCT and/or confirmation of UIP by biopsy	108 (68.4)	30 (79.0)	317 (66.0)	268 (69.6)

*In France, regulation did not permit the collection of data on race.

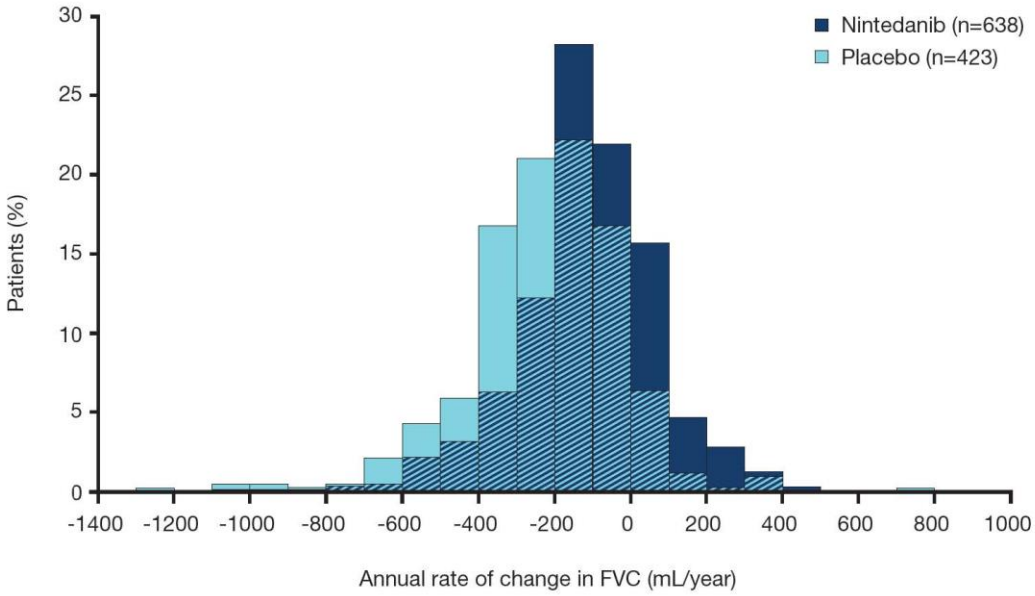
Table 2. Change in FVC (mL) from baseline of INPULSIS®-ON at week 48 in patients whose FVC improved or did not decline in INPULSIS® and in patients whose FVC declined in INPULSIS® (based on the annual rate of change in INPULSIS®)

	Patients treated with nintedanib in INPULSIS®				Patients treated with placebo in INPULSIS®*			
	Improvement or no decline in FVC in INPULSIS® (n=158)		Decline in FVC in INPULSIS® (n=480)		Improvement or no decline in FVC in INPULSIS® (n=38)		Decline in FVC in INPULSIS® (n=385)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
FVC at baseline of INPULSIS®-ON, mL	140	2913 (806)	290	2480 (732)	28	3203 (1003)	276	2568 (813)
Change in FVC from baseline of INPULSIS®-ON, mL								
Week 2	134	28 (141)	282	6 (145)	28	33 (167)	268	−2 (145)
Week 4	136	11 (162)	274	9 (144)	28	−20 (199)	263	−11 (156)
Week 6	132	13 (212)	276	8 (147)	27	−23 (200)	260	−24 (176)
Week 12	137	0 (192)	271	−14 (174)	27	−25 (129)	257	−23 (187)
Week 24	130	−35 (204)	262	−48 (183)	25	7 (157)	241	−35 (204)
Week 36	125	−30 (197)	250	−80 (213)	26	−38 (214)	224	−45 (225)
Week 48	119	−70 (246)	233	−110 (231)	24	−45 (226)	209	−76 (246)

*All patients were treated with open-label nintedanib in INPULSIS®-ON.

Figure legends

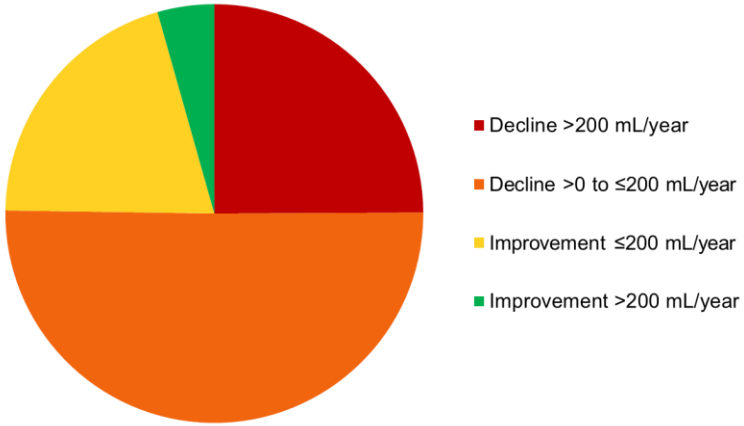
Figure 1. Annual rate of change in FVC (mL/year) in the INPULSIS® trials



Supplementary material

Figure S1. Proportions of patients with degrees of decline and improvement in FVC in the INPULSIS® trials based on annual rate of change (mL/year)

Nintedanib



Placebo

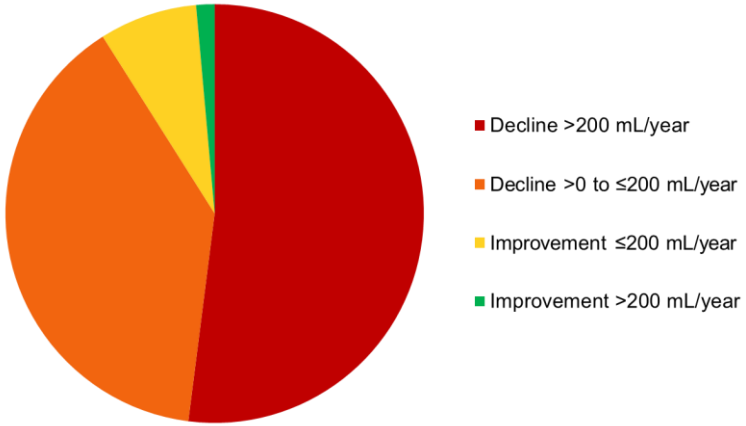


Figure S2. Baseline FVC (mL) in subgroups by annual rate of change in FVC in the INPULSIS® trials

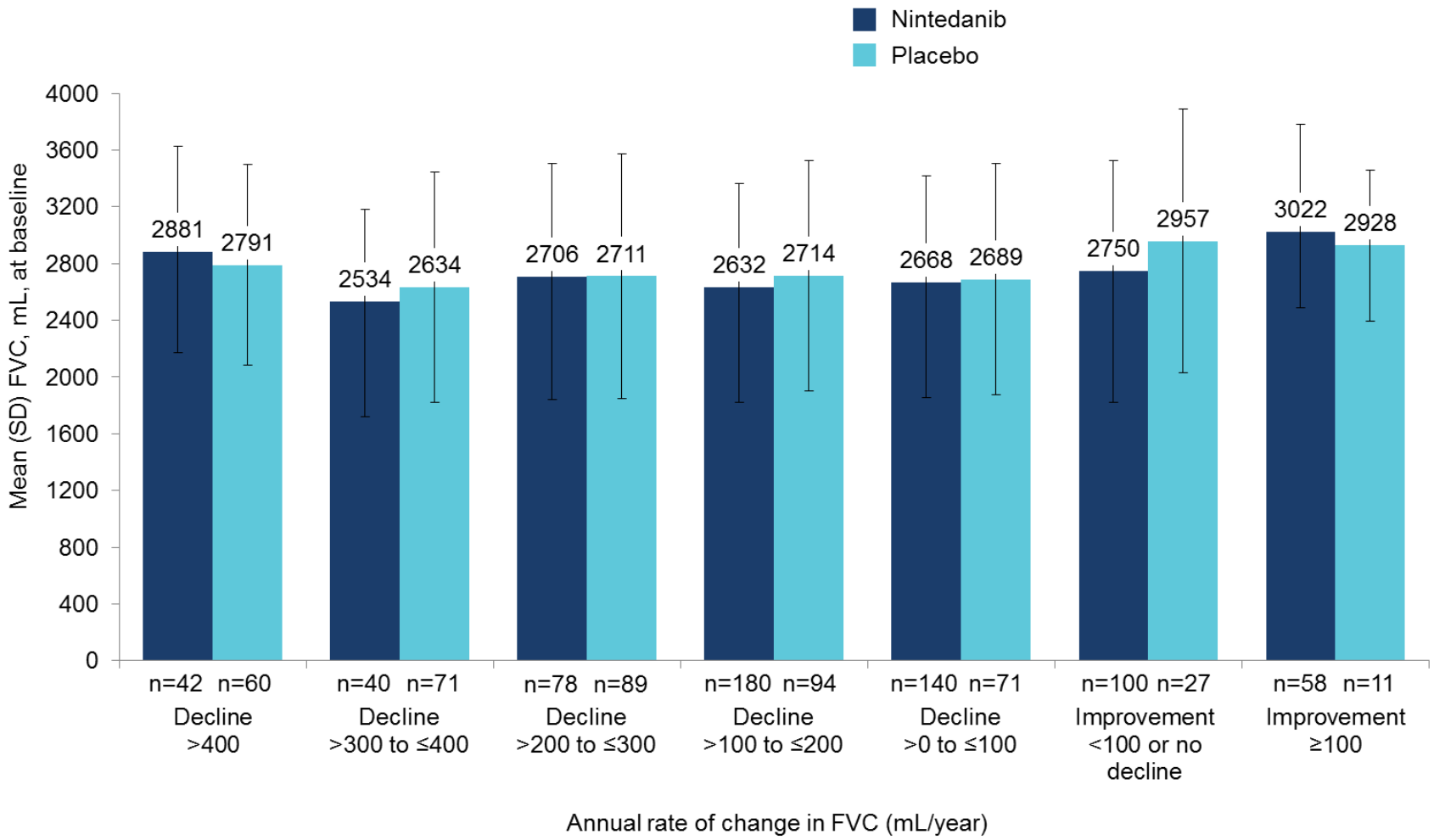


Figure S3. Baseline FVC (% predicted) in subgroups by annual rate of change in FVC in the INPULSIS® trials

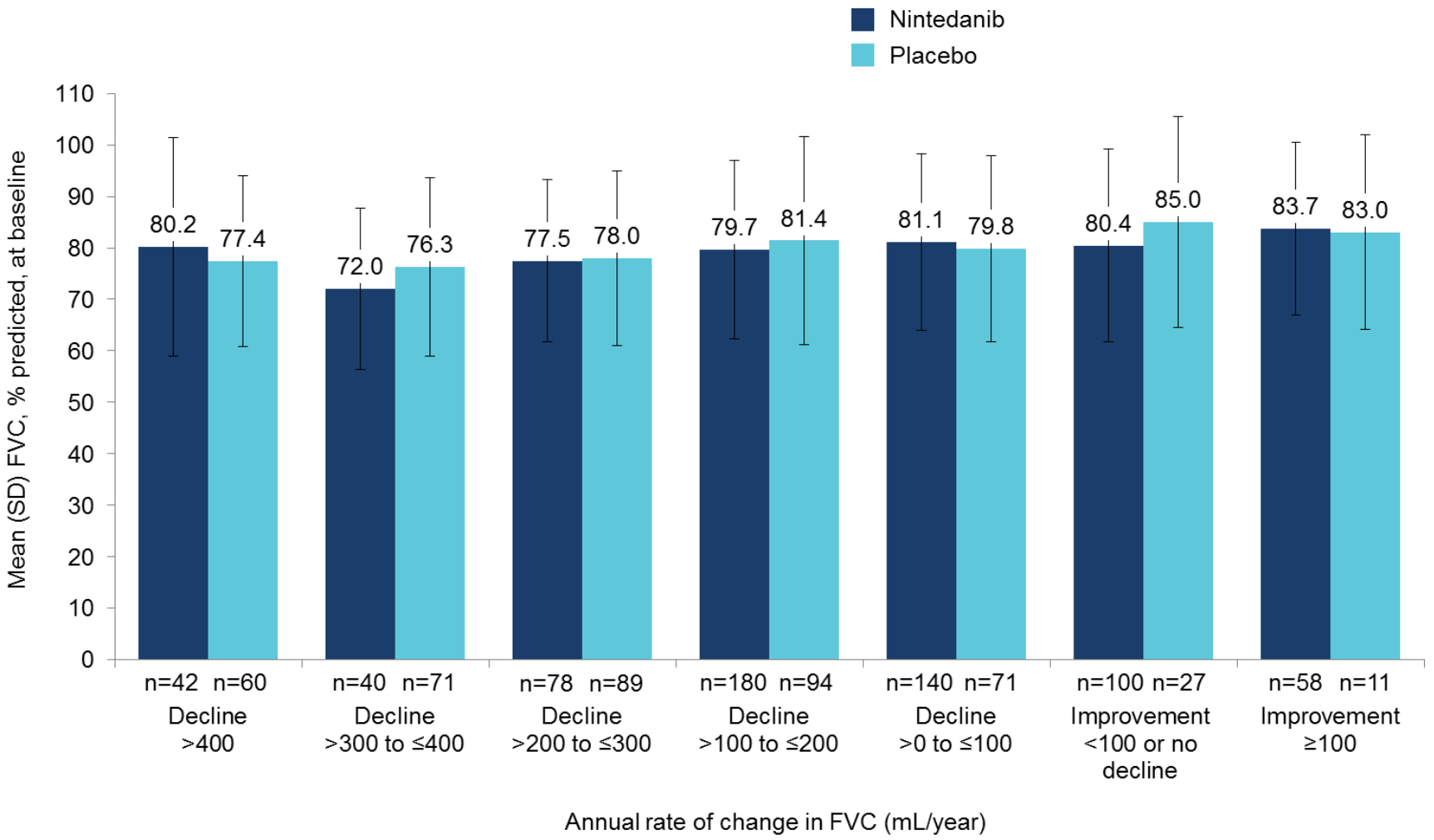


Figure S4. Baseline DLco % predicted in subgroups by annual rate of change in FVC in the INPULSIS® trials

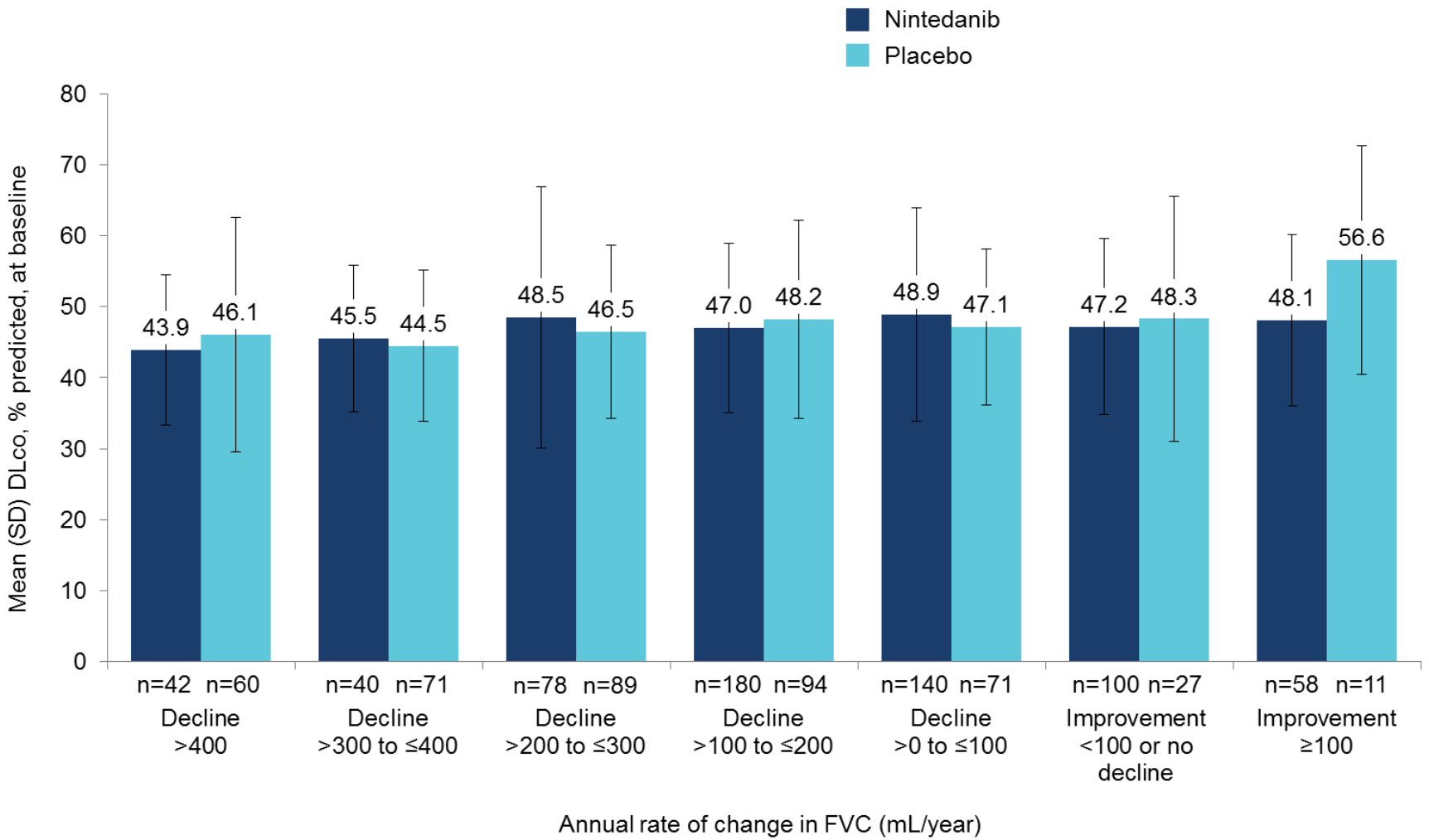


Figure S5. Proportion of patients with honeycombing on HRCT at baseline in subgroups by annual rate of change in FVC in the INPULSIS® trials

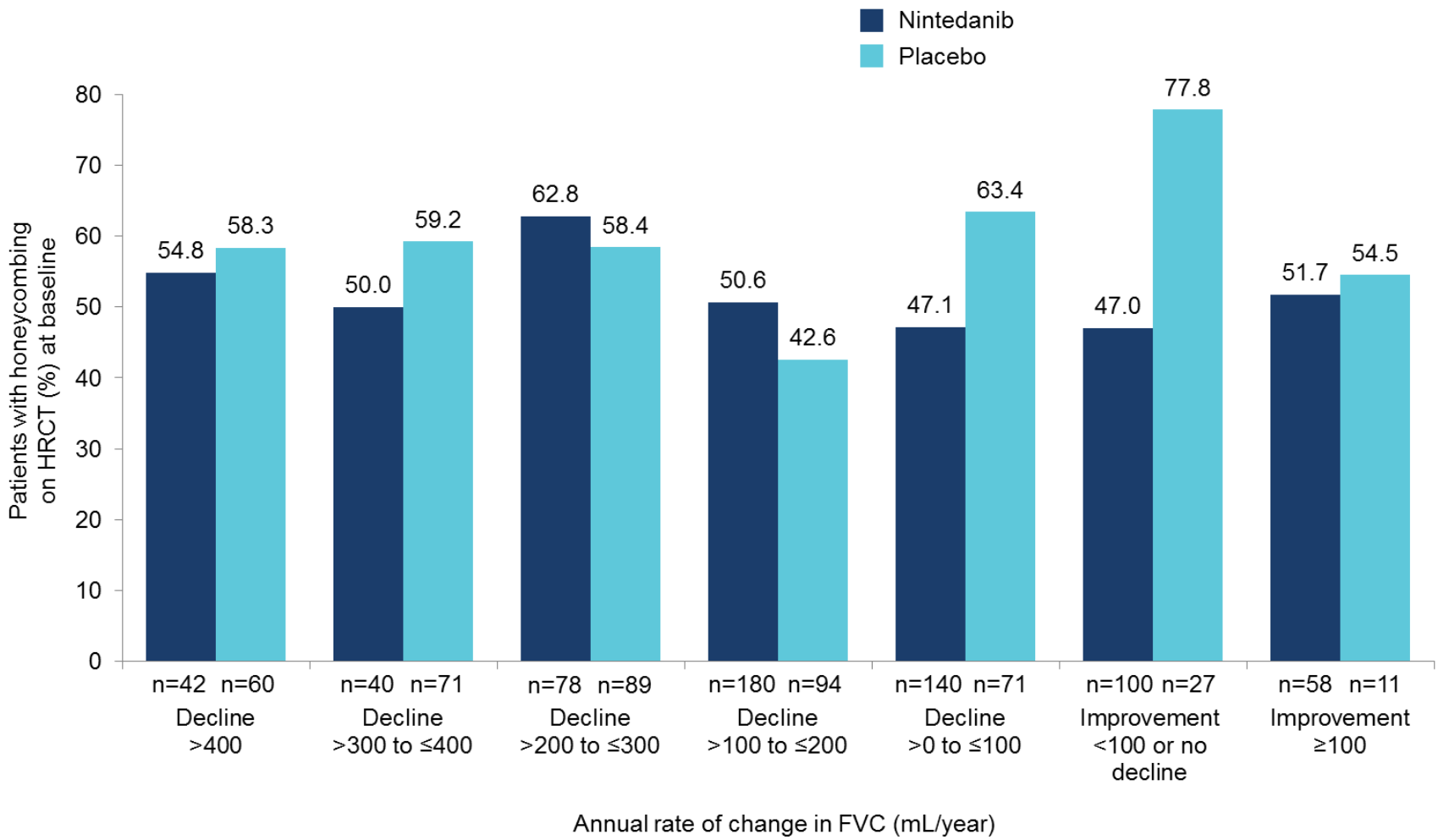


Figure S6. Change from baseline in FVC (mL) at week 52 in the INPULSIS® trials

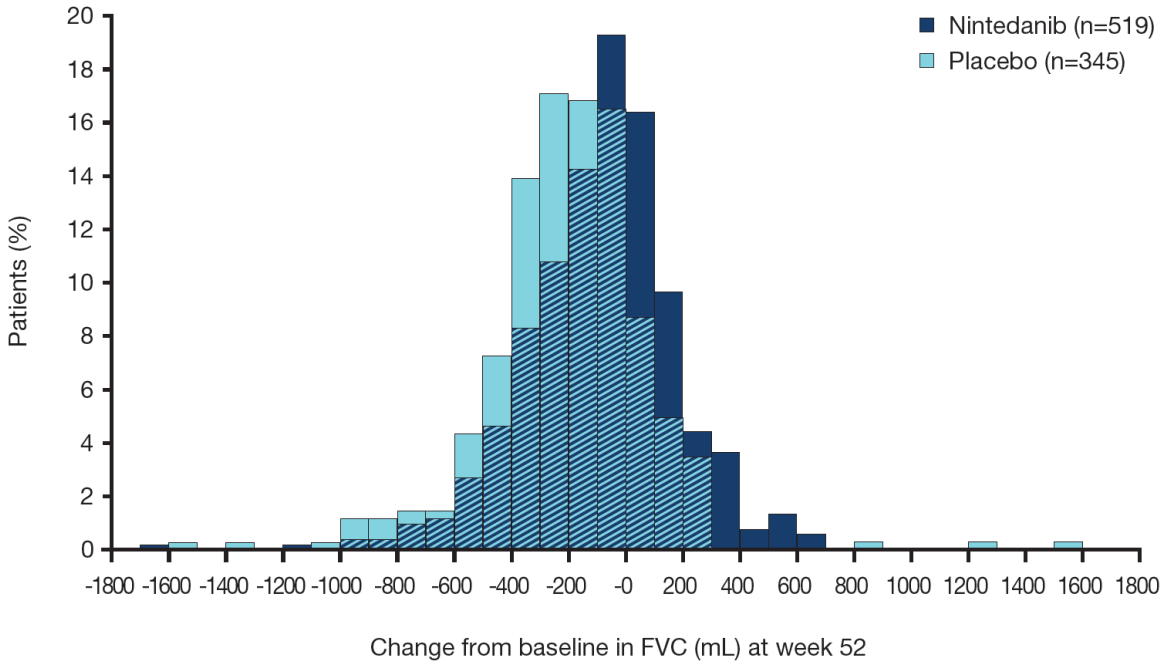


Figure S7. Change from baseline in FVC % predicted at week 52 in the INPULSIS® trials