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Effects of nintedanib by inclusion criteria for progression of interstitial lung disease

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Title: Effects of nintedanib by inclusion criteria for progression of interstitial lung disease

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Abstract

The INBUILD trial investigated nintedanib versus placebo in patients with progressive fibrosing interstitial lung diseases (ILDs). We investigated decline in forced vital capacity (FVC) in subgroups based on the inclusion criteria for ILD progression.

Subjects had a fibrosing ILD other than idiopathic pulmonary fibrosis and met these criteria for ILD progression within the 24 months before screening despite management deemed appropriate in clinical practice: Group A, relative decline in FVC $\geq 10\%$ predicted; Group B, relative decline in FVC ≥ 5 – $<10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C, worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

In the placebo group, the rates of FVC decline over 52 weeks in Groups A, B and C, respectively, were -241.9, -133.1 and -115.3 mL/year in the overall population ($p=0.0002$ for subgroup-by-time interaction) and -288.9, -156.2 and -100.1 mL/year among subjects with a usual interstitial pneumonia [UIP]-like fibrotic pattern on HRCT ($p=0.0005$ for subgroup-by-time interaction). Nintedanib had a greater absolute effect on reducing the rate of FVC decline in Group A than Group B or C. However, the relative effect of nintedanib versus placebo was consistent across the subgroups ($p>0.05$ for heterogeneity).

In conclusion, the inclusion criteria used in the INBUILD trial, based on FVC decline or worsening of symptoms and extent of fibrosis on HRCT, were effective at identifying patients with progressive fibrosing ILDs. Nintedanib reduced the rate of decline in FVC across the subgroups based on the inclusion criteria related to ILD progression.

Introduction

Fibrosing interstitial lung diseases (ILDs) have a variable clinical course. A proportion of patients with ILDs develop a progressive fibrosing phenotype characterised by decline in lung function, an increase in the extent of fibrosis on high-resolution computed tomography (HRCT), worsening symptoms, and early mortality [1–3]. There is no standard definition for progression of ILD, but a decline in forced vital capacity (FVC) $\geq 10\%$ predicted [4–8] and an increase in the extent of fibrotic abnormalities on HRCT [9–11] have been shown in studies in several ILDs to be associated with mortality. A worsening of respiratory symptoms may also be associated with mortality [12].

Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes fundamental to the progression of pulmonary fibrosis [13]. The efficacy and safety of nintedanib in subjects with progressive fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF) were investigated in the INBUILD trial [14]. To participate in this trial, subjects with fibrosing ILDs had to meet protocol-defined criteria for progression of ILD within the prior 24 months based on decline in FVC, worsening of fibrotic abnormalities on HRCT, or deterioration in symptoms. The results showed that in the overall trial population, nintedanib slowed the rate of decline in FVC (mL/year) over 52 weeks by 57% compared with placebo [14]. The criteria that should be used to define progression of fibrosing ILD in clinical trials and clinical practice, and that predict a high likelihood of worsening, remain a topic of debate. We investigated whether there were differences in the rate of decline in FVC in the placebo group, or in the treatment effect of nintedanib, in subgroups of the subjects in the INBUILD trial based on the inclusion criteria that subjects met for ILD progression.

Methods

Trial design

The design of the INBUILD trial (NCT02999178) has been described and the trial protocol is available [14]. Briefly, eligible subjects had a physician-diagnosed ILD that did not meet diagnostic criteria for IPF [15], features of diffuse fibrosing lung disease (reticular abnormality with traction bronchiectasis, with or without honeycombing) of $>10\%$ extent on HRCT, FVC $\geq 45\%$ predicted and diffusing capacity of the lungs for carbon monoxide (DLco) $\geq 30\%$ – $<80\%$ predicted. Subjects had to meet at least one of the following criteria for disease progression within the 24 months before screening, despite management deemed appropriate in clinical practice: relative decline in FVC $\geq 10\%$ predicted; relative decline in FVC $\geq 5\%$ – $<10\%$ predicted

and worsened respiratory symptoms; relative decline in FVC ≥ 5 – $<10\%$ predicted and increased extent of fibrosis on HRCT; worsened respiratory symptoms and increased extent of fibrosis on HRCT. A time frame of 24 months was chosen with the aim of enrolling patients with a broad range of fibrosing ILDs. It is important to note that at least one of these criteria needed to be met at any point *within* the 24 months before screening, not necessarily over the full 24-month period. For example, a patient who experienced a relative decline in FVC $\geq 10\%$ predicted over 6 months would have been eligible to be enrolled in the trial without waiting another 18 months. The investigators indicated which of the criteria a subject met on the case report form by ticking one or more of the boxes; this was not adjudicated.

Subjects were randomised to receive nintedanib 150 mg twice daily or placebo, stratified by fibrotic pattern on HRCT (usual interstitial pneumonia [UIP]-like fibrotic pattern or other fibrotic pattern [described in 14]). For each subject, the trial consisted of two parts: Part A, which comprised 52 weeks of treatment, and Part B, a variable treatment period beyond week 52 during which subjects continued to receive blinded treatment until all subjects had completed Part A. Subjects who discontinued treatment were asked to attend all visits as originally planned, including an end-of-treatment visit and a follow-up visit 4 weeks later. The second (final) database lock took place after all subjects had completed the follow-up visit or had entered the open-label extension trial (INBUILD-ON; NCT03820726). Data from up to the second (final) database lock comprised the data from the whole trial.

Analyses

Subjects were grouped into mutually exclusive categories based on the inclusion criteria for ILD progression: Group A, relative decline in FVC $\geq 10\%$ predicted; Group B, relative decline in FVC ≥ 5 – $<10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C, worsened respiratory symptoms and increased extent of fibrosis on HRCT only. Subjects who had a relative decline in FVC $\geq 10\%$ predicted were included in Group A irrespective of whether another box had been ticked. Subjects who had a relative decline in FVC ≥ 5 – $<10\%$ predicted as well as worsened respiratory symptoms and/or increased extent of fibrosis on HRCT were included in Group B. Thus Group C comprised subjects for whom *only* the box for worsened respiratory symptoms and increased extent of fibrosis on HRCT had been ticked.

In Groups A, B and C, we analysed the rate of decline in FVC (mL/year) in the placebo group, the rate of decline in FVC (mL/year) over 52 weeks with nintedanib versus placebo, and the relative effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52

weeks. These analyses were performed in the overall population, in subjects with a UIP-like fibrotic pattern on HRCT, and in subjects with other fibrotic patterns on HRCT. In Groups A, B and C, we analysed the time to first acute exacerbation of ILD (defined in [14]) or death, time to death, and time to progression of ILD (absolute decline in FVC $\geq 10\%$ predicted) or death over the whole trial in the overall population only.

The rate of decline in FVC (mL/year) over 52 weeks in the placebo group in the overall population was analysed using a random coefficient regression model (with random slopes and intercepts) including baseline FVC (mL), HRCT pattern (UIP-like fibrotic pattern or other fibrotic patterns), and baseline-by-time and subgroup-by-time interactions. The rate of decline in FVC (mL/year) over 52 weeks with nintedanib versus placebo in the overall population was analysed using a random coefficient regression model (with random slopes and intercepts) including baseline FVC (mL), HRCT pattern, and baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions. The same models were used for analyses in subjects with a UIP-like fibrotic pattern and in subjects with other fibrotic patterns on HRCT except that HRCT pattern was not included as a term. Nominal p-values for interactions were obtained from tests of heterogeneity across the subgroups, with no adjustment for multiple testing. The relative effect (%) of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks was analysed using fixed effect and random effects meta-analyses, where the relative treatment effect was calculated as the absolute treatment effect normalised by the adjusted rate of decline in FVC in the placebo group. P-values for heterogeneity were calculated using Cochran's Q-Test. Time to first acute exacerbation of ILD or death, time to death, and time to progression of ILD or death over the whole trial were analysed using a stratified log-rank test stratified by HRCT pattern. A Cox regression model with a term for treatment was used to derive the hazard ratio and 95% CI, and p-values for treatment-by-subgroup interactions were obtained from a Cox regression model with terms for treatment, subgroup and treatment-by-subgroup, stratified by HRCT pattern. Adverse events in Groups A, B and C are presented descriptively. Analyses of the rate of decline in FVC (mL/year) over 52 weeks with nintedanib versus placebo and of adverse events in subgroups by inclusion criteria for ILD progression in the co-primary analysis populations were pre-specified; the other analyses presented were performed post-hoc.

Results

Subjects

Of 663 subjects in the overall population, 332 (50.1%) were included in Group A, 207 (31.2%) in Group B and 123 (18.6%) in Group C; one patient had missing information. Of 412 subjects with

a UIP-like fibrotic pattern on HRCT, 198 (48.1%) were included in Group A, 144 (35.0%) in Group B and 69 (16.7%) in Group C; one patient had missing information. Of 251 subjects with other fibrotic patterns on HRCT, 134 (53.4%) were included in Group A, 63 (25.1%) in Group B and 54 (21.5%) in Group C. In the overall population, baseline characteristics were generally similar across the subgroups by criteria for ILD progression, although FVC % predicted was slightly lower in Group A than in Groups B and C (Table 1).

Rate of decline in FVC (mL/year) over 52 weeks by inclusion criteria for ILD progression

In the placebo group, the rate of decline in FVC over 52 weeks in the overall population was greater among subjects in Group A (-241.9 mL/year) than in Group B (-133.1 mL/year) or Group C (-115.3 mL/year) ($p=0.0002$ for subgroup-by-time interaction) (Figure 1A). Similarly, in placebo-treated subjects with a UIP-like fibrotic pattern on HRCT, the rate of decline in FVC over 52 weeks was greater among subjects in Group A (-288.9 mL/year) than in Group B (-156.2 mL/year) or Group C (-100.1 mL/year) ($p=0.0005$ for subgroup-by-time interaction) (Figure 1B). In placebo-treated subjects with other fibrotic patterns on HRCT, the rate of decline in FVC over 52 weeks was numerically greater in Group A than in Group B or Group C, but the interaction p-value did not indicate heterogeneity across the subgroups ($p=0.089$ for subgroup-by-time interaction) (Figure 1C).

In the overall population and in subjects with a UIP-like fibrotic pattern on HRCT, the treatment-by-subgroup-by-time interaction p-values (0.026 and 0.039, respectively) indicated a heterogeneous treatment effect of nintedanib on reducing the rate of decline in FVC across the groups, with a greater effect of nintedanib versus placebo in Group A than in Group B or Group C (Table 2). However, analyses of the relative treatment effect, based on absolute treatment effects normalised by the adjusted rate of decline in FVC in the placebo group, did not indicate a heterogeneous treatment effect of nintedanib on reducing the rate of decline in FVC across the subgroups (Figure 2).

Progression events over the whole trial by inclusion criteria for ILD progression

The proportion of subjects who had an acute exacerbation of ILD or death, who died, and who had progression of ILD (absolute decline in FVC $\geq 10\%$ predicted) or death over the whole trial was lower in subjects treated with nintedanib than placebo in all the subgroups by inclusion criteria for ILD progression, with no evidence of heterogeneity across the subgroups (Table 3).

Adverse events by inclusion criteria for ILD progression

The adverse events associated with nintedanib were similar across the subgroups by inclusion criteria for ILD progression (Supplementary Table S1). The most frequent adverse event associated with nintedanib was diarrhoea. Nausea, vomiting, decreased appetite and weight decrease were also more frequently reported in subjects treated with nintedanib than placebo. In the nintedanib and placebo groups, respectively, adverse events led to permanent discontinuation of trial drug in 20.6% and 12.8% of subjects in Group A, 23.6% and 8.2% in Group B and 9.7% and 6.6% in Group C (Supplementary Table S1).

Discussion

The INBUILD trial enrolled subjects with fibrosing ILDs other than IPF, who had demonstrated progression of ILD within the prior 24 months based on a decline in FVC $\geq 10\%$ predicted, a decline in FVC $\geq 5\text{--}<10\%$ predicted with worsened symptoms and/or an increased extent of fibrosis on HRCT, or worsened respiratory symptoms and an increased extent of fibrosis on HRCT only. Previous analyses of data from the placebo group of the INBUILD trial had demonstrated there was a marked decline in FVC over the 52 weeks of the trial, with a greater rate of decline in FVC in subjects with a UIP-like fibrotic pattern on HRCT than in subjects with other fibrotic patterns on HRCT [16] and no evidence of heterogeneity across subgroups by ILD diagnosis [17]. These new analyses have shown that the rate of decline in FVC over 52 weeks was greater in subjects who had experienced a decline in FVC $\geq 10\%$ predicted within the 24 months prior to entering the trial than in subjects who met other inclusion criteria for ILD progression. That said, it should be noted that all the subgroups based on inclusion criteria for ILD progression experienced a marked decline in FVC over 52 weeks. Even in Group C, which showed the lowest rate of decline in FVC over 52 weeks, the rate of decline in FVC was -127.5 mL/year.

Data on FVC decline as a predictor of the trajectory of FVC in patients with fibrosing ILDs other than IPF are very limited. A number of retrospective studies have suggested that decline in FVC is a poor predictor of future decline in FVC in patients with IPF, despite being associated with mortality [21–24]. However, the methodological limitations of such studies must be considered [25]. A prospective study based on home spirometry found that in the majority of patients, decline in FVC was almost linear [26]. A recent analysis of data from 826 patients with SSc-ILD in the EUSTAR database showed that patterns of change in FVC were inconsistent between consecutive 12-month periods, with periods of marked progression (decline in FVC $>10\%$ predicted) mostly followed by periods of stability [27].

Although there is no established definition for progression of fibrosing ILD, a number of sets of criteria have been proposed [8, 14, 28–30]. Identifying patients with progressive ILD in clinical practice is likely most effectively achieved based on a multi-dimensional approach, taking into account physiological data, radiological changes, and symptoms. The results of the INBUILD trial suggest that although other inclusion criteria might have been chosen, the criteria used in this trial were effective at identifying patients with progressive ILD who would continue to progress over the following year. Although visual assessment of ILD progression on HRCT over short periods can be unreliable, a few previous studies have shown that worsening fibrotic abnormalities on HRCT, in the absence of documented decline in FVC, are predictive of worse decline in FVC in patients with fibrosing ILDs [18–20]. Our data support these findings, highlighting the need for close monitoring of patients who show a worsening of fibrosis on HRCT in clinical practice.

While the absolute effect of nintedanib was lower in the other subgroups than in patients in whom the investigator had noted a relative decline in FVC $\geq 10\%$ predicted within the previous 24 months, the relative effect of nintedanib on reducing the rate of decline in FVC, and the risk of events reflecting progression of ILD, was consistent across the subgroups. This supports previous analyses of data from the INBUILD trial showing that nintedanib had a consistent effect on slowing the progression of ILD across subgroups based on fibrotic pattern on HRCT [14], ILD diagnosis [17] and severity of FVC impairment at baseline [31]. The adverse event profile of nintedanib was also consistent across the subgroups, consistent with previous subgroup analyses of the INBUILD trial [14, 17, 31] and the established safety profile of nintedanib in patients with fibrosing ILDs.

The INBUILD trial was designed to enrol subjects with fibrosing ILDs who had been identified in clinical practice as having a progressive phenotype despite management deemed appropriate for that ILD. The investigators were asked to indicate which of the inclusion criteria for ILD progression a subject met, but not to provide details or documentation of the course of that subject's ILD over the prior 24 months. These inclusion criteria reflect current clinical practice, in which a clinician makes a decision on whether a patient with fibrosing ILD is progressing based on their interpretation of the evidence available to them. However, this design confers limitations to our analyses in that we are unable to characterise the prior course of ILD in the subgroups based on inclusion criteria for ILD progression, or to be sure that these subgroups were mutually exclusive. For example, a subject may have been entered into Group C based on the investigator having no evidence of an FVC decline of $\geq 5\%$ predicted within the prior 24 months when in fact such a decline in FVC had occurred but had not been documented. As no data on

the progression of ILD prior to subjects entering the INBUILD trial were collected, we are unable to investigate more specific subgroups than were covered by the inclusion criteria; for example, we are unable to investigate whether subjects who had a decline in FVC $\geq 10\%$ predicted over the prior 24 months had a greater decline in FVC during the trial than subjects who had a decline in FVC $\geq 10\%$ predicted over the prior 6 months. It should be noted that the INBUILD trial was not designed or powered to investigate these subgroups.

In conclusion, the current analyses suggest that the inclusion criteria used in the INBUILD trial, based on decline in FVC or worsening symptoms and extent of fibrosis on HRCT, were effective at identifying patients with fibrosing ILDs who had a progressive phenotype. These criteria are straightforward to assess in clinical practice, suggesting that they may have utility in facilitating the prompt identification of patients with fibrosing ILDs that have progressed who are at risk of further progression and should be considered for treatment.

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TABLE 1. Baseline characteristics in subgroups in the overall population by inclusion criteria for ILD progression.

	Group A		Group B		Group C	
	Nintedanib (n=160)	Placebo (n=172)	Nintedanib (n=110)	Placebo (n=97)	Nintedanib (n=62)	Placebo (n=61)
Male	81 (50.6)	85 (49.4)	66 (60.0)	53 (54.6)	32 (51.6)	38 (62.3)
Age, years	66.5 (9.0)	67.2 (9.1)	64.8 (9.6)	66.0 (9.3)	62.8 (11.2)	64.1 (12.1)
Body mass index (kg/m ²)	27.9 (5.2)	28.0 (5.5)	28.1 (4.8)	28.9 (5.8)	28.8 (5.1)	28.8 (5.1)
ILD diagnosis						
Hypersensitivity pneumonitis	44 (27.5)	51 (29.7)	24 (21.8)	27 (27.8)	16 (25.8)	11 (18.0)
Autoimmune ILDs*	43 (26.9)	42 (24.4)	26 (23.6)	31 (32.0)	13 (21.0)	15 (24.6)
Idiopathic NSIP	30 (18.8)	32 (18.6)	16 (14.5)	16 (16.5)	18 (29.0)	13 (21.3)
Unclassifiable IIP	30 (18.8)	25 (14.5)	26 (23.6)	14 (14.4)	8 (12.9)	11 (18.0)
Other ILDs [†]	13 (8.1)	22 (12.8)	18 (16.4)	9 (9.3)	7 (11.3)	11 (18.0)
UIP-like fibrotic pattern on HRCT	100 (62.5)	98 (57.0)	76 (69.1)	68 (70.1)	30 (48.4)	39 (63.9)
FVC (mL)	2210 (706)	2121 (633)	2452 (705)	2487 (752)	2477 (837)	2601 (772)
FVC % predicted	66.5 (14.8)	65.6 (12.7)	70.0 (16.3)	73.4 (16.8)	72.1 (17.9)	73.0 (16.8)
DLco % predicted	44.8 (12.3)	45.1 (13.2)	43.5 (11.7)	51.8 (15.4)	44.7 (11.6)	49.5 (17.4)

Data are n (%) or mean (SD). Group A: decline in FVC $\geq 10\%$ predicted; Group B: decline in FVC ≥ 5 – $<10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C: worsened respiratory symptoms and increased extent of fibrosis on HRCT only. *Included rheumatoid arthritis associated-ILD, systemic sclerosis associated-ILD, mixed connective tissue disease associated-ILD, plus subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of case report form. †Included sarcoidosis, exposure-related ILDs and selected terms in the “Other fibrosing ILDs” category of case report form. DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

TABLE 2. Rate of decline in FVC (mL/year) over 52 weeks with nintedanib versus placebo by inclusion criteria for ILD progression.

	Group A		Group B		Group C	
	Nintedanib (n=160)	Placebo (n=172)	Nintedanib (n=110)	Placebo (n=97)	Nintedanib (n=62)	Placebo (n=61)
Overall population						
N analysed	160	172	110	97	62	61
Adjusted mean (SE) rate of decline in FVC (mL/year)	-72.5 (21.8)	-235.0 (20.8)	-109.5 (26.0)	-145.3 (27.5)	-49.7 (34.3)	-127.5 (33.8)
Difference vs placebo (95% CI)	162.5 (103.5, 221.4)		35.8 (-38.4, 109.9)		77.8 (-16.5, 172.0)	
Treatment-by-subgroup-by-time interaction	p=0.026					
Subjects with a UIP-like fibrotic pattern on HRCT						
N analysed	100	98	76	68	30	39
Adjusted mean (SE) rate of decline in FVC (mL/year)	-68.7 (29.7)	-279.4 (30.0)	-117.3 (34.0)	-172.7 (35.9)	-40.9 (54.4)	-114.4 (46.0)
Difference vs placebo (95% CI)	210.7 (128.0, 293.4)		55.4 (-41.7, 152.5)		73.6 (-65.5, 212.7)	
Treatment-by-subgroup-by-time interaction	p=0.039					

Subjects with other fibrotic patterns on HRCT

N analysed	60	74	34	29	32	22
Adjusted mean (SE) rate of decline in FVC (mL/year)	-79.4 (31.9)	-182.7 (28.2)	-99.2 (41.4)	-91.3 (43.8)	-55.6 (42.3)	-145.9 (49.7)
Difference vs placebo (95% CI)	103.3 (19.7, 186.9)		-8.0 (-126.1, 110.2)		90.3 (-38.3, 218.9)	
Treatment-by-subgroup-by-time interaction	p=0.30					

Group A: decline in FVC $\geq 10\%$ predicted; Group B: decline in FVC ≥ 5 — $< 10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C: worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

TABLE 3. Time to first acute exacerbation of ILD or death, time to death and time to progression of ILD (absolute decline in FVC $\geq 10\%$ predicted) or death over the whole trial in the overall population by inclusion criteria for ILD progression.

	Group A		Group B		Group C	
	Nintedanib (n=160)	Placebo (n=172)	Nintedanib (n=110)	Placebo (n=97)	Nintedanib (n=62)	Placebo (n=61)
Time to first acute exacerbation of ILD or death						
Subjects with event, n (%)	23 (14.4)	39 (22.7)	15 (13.6)	17 (17.5)	8 (12.9)	9 (14.8)
Hazard ratio (95% CI)	0.59 (0.35, 0.99)		0.73 (0.36, 1.47)		0.80 (0.30, 2.18)	
Treatment-by-subgroup interaction	p=0.67					
Time to death						
Deaths, n (%)	20 (12.5)	27 (15.7)	9 (8.2)	11 (11.3)	7 (11.3)	7 (11.5)
Hazard ratio (95% CI)	0.77 (0.43, 1.37)		0.65 (0.27, 1.58)		0.97 (0.32, 2.92)	
Treatment-by-subgroup interaction	p=0.70					
Time to progression of ILD (absolute decline in FVC ≥10% predicted) or death						
Subjects with event, n (%)	67 (41.9)	102 (59.3)	42 (38.2)	48 (49.5)	25 (40.3)	31 (50.8)
Hazard ratio (95% CI)	0.60 (0.44, 0.81)		0.72 (0.47, 1.09)		0.79 (0.46, 1.34)	
Treatment-by-subgroup interaction	p=0.59					

Group A: decline in FVC $\geq 10\%$ predicted; Group B: decline in FVC ≥ 5 – $<10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C: worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

FIGURE LEGENDS

FIGURE 1. Rate of decline in FVC (mL/year) over 52 weeks in the placebo group by criteria for ILD progression in (A) the overall population, (B) subjects with a UIP-like fibrotic pattern on HRCT and (C) subjects with other fibrotic patterns on HRCT.

FIGURE 2. Relative effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) over 52 weeks by inclusion criteria for ILD progression in (A) the overall population, (B) subjects with a UIP-like fibrotic pattern on HRCT and (C) subjects with other fibrotic patterns on HRCT.

p=0.0002 for subgroup-by-time interaction.

p=0.0005 for subgroup-by-time interaction.

p=0.089 for subgroup-by-time interaction.

p=0.31 for heterogeneity based on Cochran's Q-Test.

p=0.41 for heterogeneity based on Cochran's Q-Test.

p=0.62 for heterogeneity based on Cochran's Q-Test

ONLINE SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Adverse events in the overall population by inclusion criteria for ILD progression.

	Group A		Group B		Group C	
	Nintedanib (n=160)	Placebo (n=172)	Nintedanib (n=110)	Placebo (n=97)	Nintedanib (n=62)	Placebo (n=61)
Any adverse event(s)	152 (95.0)	158 (91.9)	104 (94.5)	85 (87.6)	61 (98.4)	52 (85.2)
Most frequent adverse events*						
Diarrhoea	107 (66.9)	31 (18.0)	71 (64.5)	33 (34.0)	44 (71.0)	15 (24.6)
Nausea	50 (31.3)	10 (5.8)	33 (30.0)	15 (15.5)	13 (21.0)	6 (9.8)
Bronchitis	23 (14.4)	21 (12.2)	14 (12.7)	16 (16.5)	4 (6.5)	9 (14.8)
Cough	14 (8.8)	23 (13.4)	9 (8.2)	14 (14.4)	10 (16.1)	6 (9.8)
Vomiting	33 (20.6)	5 (2.9)	23 (20.9)	9 (9.3)	5 (8.1)	3 (4.9)
Decreased appetite	21 (13.1)	9 (5.2)	15 (13.6)	5 (5.2)	12 (19.4)	3 (4.9)
Weight decreased	21 (13.1)	6 (3.5)	10 (9.1)	2 (2.1)	10 (16.1)	3 (4.9)
ALT increased	28 (17.5)	7 (4.1)	12 (10.9)	2 (2.1)	3 (4.8)	3 (4.9)
Progression of ILD [†]	8 (5.0)	27 (15.7)	7 (6.4)	8 (8.2)	1 (1.6)	4 (6.6)
Serious adverse event(s) [‡]	54 (33.8)	70 (40.7)	36 (32.7)	27 (27.8)	17 (27.4)	13 (21.3)
Fatal adverse event	7 (4.4)	10 (5.8)	3 (2.7)	6 (6.2)	1 (1.6)	1 (1.6)

Adverse event(s) leading to permanent treatment discontinuation	33 (20.6)	22 (12.8)	26 (23.6)	8 (8.2)	6 (9.7)	4 (6.6)
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Data are n (%) of subjects with ≥ 1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake in subjects who discontinued trial drug before week 52). Group A: decline in FVC $\geq 10\%$ predicted; Group B: decline in FVC ≥ 5 – $<10\%$ predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; Group C: worsened respiratory symptoms and increased extent of fibrosis on HRCT only. *Adverse events reported in $>15\%$ of subjects in any group, coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). [†]Corresponded to MedDRA preferred term “interstitial lung disease”. [‡]Adverse events that resulted in death, were life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed to be serious for any other reason. ALT, alanine aminotransferase; ILD, interstitial lung disease.