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

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In the INBUILD trial in patients with fibrosing ILDs, the relative effect of nintedanib *versus* placebo on reducing the rate of FVC decline was consistent across subgroups based on the criteria regarding ILD progression that patients fulfilled on trial entry https://bit.ly/35jpOiE

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Abstract

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

Methods Subjects had a fibrosing ILD other than idiopathic pulmonary fibrosis and met the following criteria for ILD progression within the 24 months before screening despite management deemed appropriate in clinical practice: Group A, relative decline in FVC ⩾10% predicted; Group B, relative decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on high-resolution computed tomography (HRCT); Group C, worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

Results 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 per year in the overall population (p=0.0002 for subgroup-by-time interaction) and −288.9, −156.2 and −100.1 mL per 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 in Group B or C. However, the relative effect of nintedanib *versus* placebo was consistent across the subgroups (p>0.05 for heterogeneity).

Conclusions 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 studies in several ILDs have shown that a decline in forced vital capacity (FVC) ⩾10% predicted [4–8] and an increase in the extent of fibrotic abnormalities on HRCT [9–11] are 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 per 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 subjects in the INBUILD trial based on the inclusion criteria that these 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 ⩾45% predicted and diffusing capacity of the lungs for carbon monoxide (D_{LCO}) ⩾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 ⩾10% predicted, relative decline in FVC ⩾5–<10% predicted and worsened respiratory symptoms, relative decline in FVC ⩾5–<10% predicted and increased extent of fibrosis on HRCT, or worsened respiratory symptoms and increased extent of fibrosis on HRCT. A timeframe 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 during the 24 months before screening, not necessarily over the full 24-month period. For example, a patient who experienced a relative decline in FVC ⩾10% predicted over 6 months would have been eligible for enrolment 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. The trial was carried out in compliance with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation. The trial was approved by an ethics committee or institutional review board at every participating site.

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

All subjects were grouped into mutually exclusive categories based on the inclusion criteria for ILD progression: Group A, relative decline in FVC ⩾10% predicted; Group B, relative decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; or Group C, worsened respiratory symptoms and increased extent of fibrosis on HRCT only. Subjects who had a relative decline in FVC ⩾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 per year) in the placebo group, the rate of decline in FVC (mL per year) over 52 weeks with nintedanib *versus* placebo and the relative effect of nintedanib *versus* placebo on the rate of decline in FVC (mL per 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 ⩾10% predicted) or death over the whole trial in the overall population only.

The rate of decline in FVC (mL per 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 per 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 per year) over 52 weeks was analysed using fixed-effect and random-effects meta-analyses, in which 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 ratios and 95% confidence intervals, 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 per 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*.

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

	Group A[#]		Group B[¶]		Group C[+]	
	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Placebo
Subjects, n	160	172	110	97	62	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[f]	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
D_{LCO} % 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 presented as n (%) or mean±SD, unless otherwise stated. ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: decline in FVC ⩾10% predicted; [¶]: decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; [+]: worsened respiratory symptoms and increased extent of fibrosis on HRCT only; [§]: included rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD and mixed connective tissue disease-associated ILD, plus subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of case report form; [f]: included sarcoidosis, exposure-related ILDs and selected terms in the "Other fibrosing ILDs" category of case report form.

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

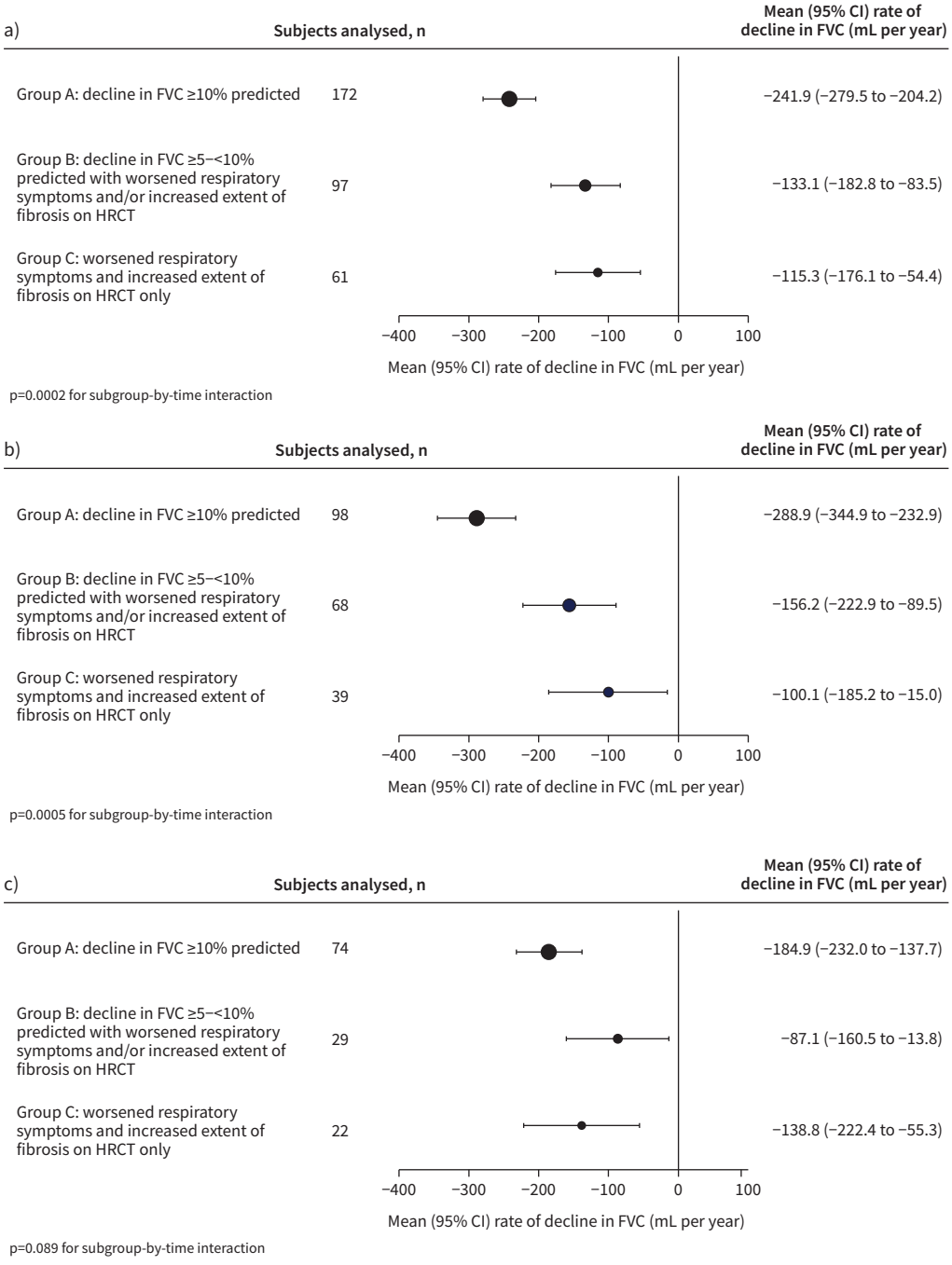

FIGURE 1 Rate of decline in forced vital capacity (FVC) (mL per year) over 52 weeks in the placebo group by criteria for interstitial lung disease progression in a) the overall population, b) subjects with a usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography (HRCT) and c) subjects with other fibrotic patterns on HRCT.

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 per 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 per year) than in Group B (−133.1 mL per year) or Group C (−115.3 mL per 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 per year) than in Group B (−156.2 mL per year) or Group C (−100.1 mL per 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 died, who died, and who had progression of ILD (absolute decline in FVC ⩾10% predicted) or died 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 the 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).

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

	Group A[#]		Group B[¶]		Group C[+]	
	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib	Placebo
Overall population						
Subjects analysed, n	160	172	110	97	62	61
Adjusted mean±SE rate of decline in FVC, mL per year	−72.±21.8	−235.0±20.8	−109.5±26.0	−145.3±27.5	−49.7±34.3	−127.5±33.8
Difference *versus* placebo (95% CI)	162.5 (103.5 to 221.4)		35.8 (−38.4 to 109.9)		77.8 (−16.5 to 172.0)	
Treatment-by-subgroup-by-time interaction	p=0.026					
Subjects with a UIP-like fibrotic pattern on HRCT						
Subjects analysed, n	100	98	76	68	30	39
Adjusted mean±SE rate of decline in FVC, mL per 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 *versus* placebo (95% CI)	210.7 (128.0 to 293.4)		55.4 (−41.7 to 152.5)		73.6 (−65.5 to 212.7)	
Treatment-by-subgroup-by-time interaction	p=0.039					
Subjects with other fibrotic patterns on HRCT						
Subjects analysed, n	60	74	34	29	32	22
Adjusted mean±SE rate of decline in FVC, mL per 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 *versus* placebo (95% CI)	103.3 (19.7 to 186.9)		−8.0 (−126.1 to 110.2)		90.3 (−38.3 to 218.9)	
Treatment-by-subgroup-by-time interaction	p=0.30					

FVC: forced vital capacity; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography. [#]: decline in FVC ⩾10% predicted; [¶]: decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; [+]: worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

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 ⩾10% predicted, a decline in FVC ⩾5–<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 demonstrated that 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

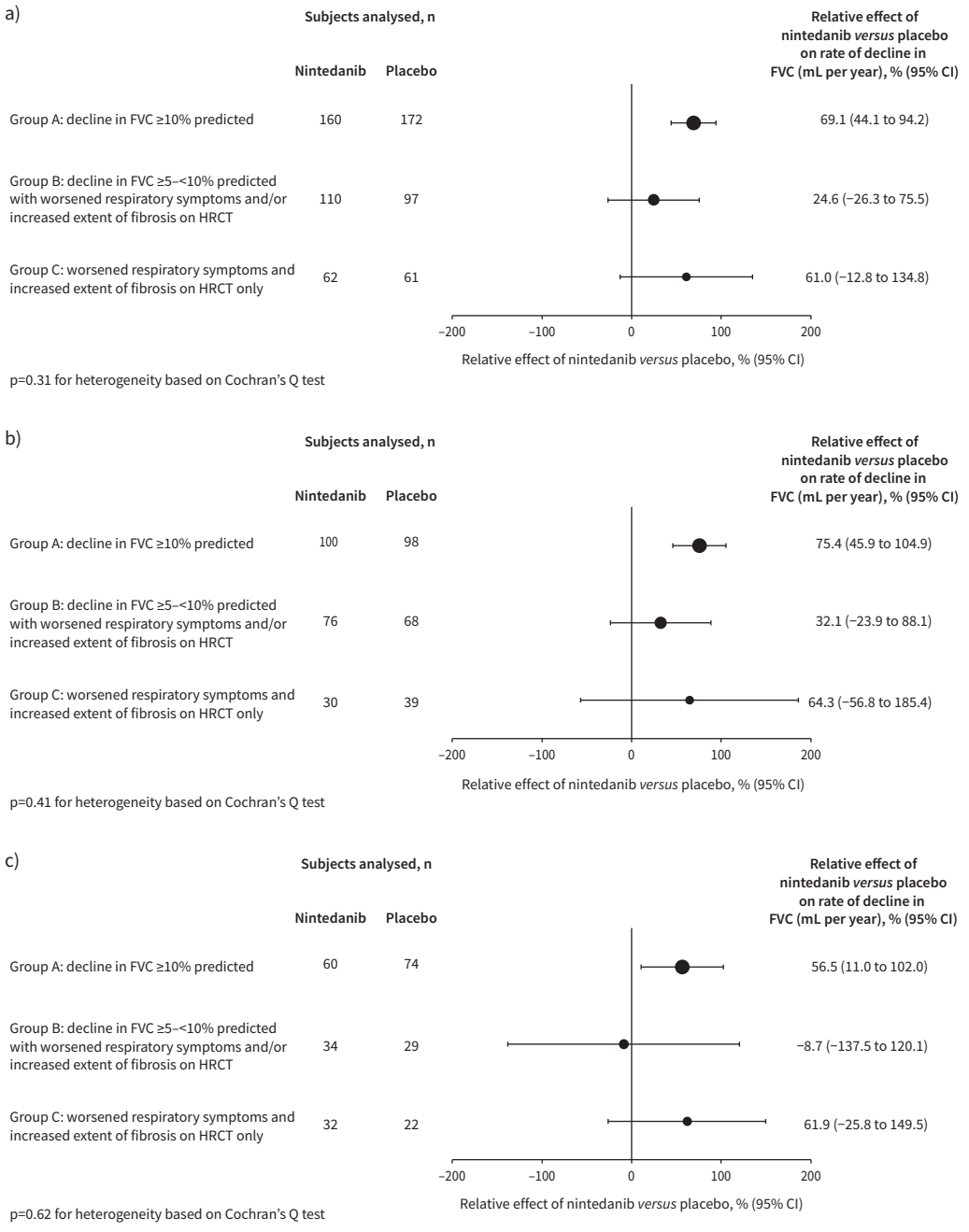

FIGURE 2 Relative effect of nintedanib *versus* placebo on the rate of decline in forced vital capacity (FVC) (mL per year) over 52 weeks by inclusion criteria for interstitial lung disease progression in a) the overall population, b) subjects with a usual interstitial pneumonia-like fibrotic pattern on high-resolution computed tomography (HRCT) and c) subjects with other fibrotic patterns on HRCT.

TABLE 3 Time to first acute exacerbation of ILD or death, time to death and time to progression of ILD (absolute decline in FVC ⩾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	Placebo	Nintedanib	Placebo	Nintedanib	Placebo
Subjects, n	160	172	110	97	62	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 to 0.99)		0.73 (0.36 to 1.47)		0.80 (0.30 to 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 to 1.37)		0.65 (0.27 to 1.58)		0.97 (0.32 to 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 to 0.81)		0.72 (0.47 to 1.09)		0.79 (0.46 to 1.34)	
Treatment-by-subgroup interaction	p=0.59					

ILD: interstitial lung disease; FVC: forced vital capacity. [#]: decline in FVC ⩾10% predicted; [¶]: decline in FVC ⩾5–<10% predicted with worsened respiratory symptoms and/or increased extent of fibrosis on HRCT; [+]: worsened respiratory symptoms and increased extent of fibrosis on HRCT only.

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 ⩾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 per 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 [18–21]. However, the methodological limitations of such studies must be considered [22]. A prospective study based on home spirometry found that in the majority of patients, decline in FVC was almost linear [23]. A recent analysis of data from 826 patients with systemic sclerosis-associated 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 [24].

Although there is no established definition for progression of fibrosing ILD, a number of sets of criteria have been proposed [8, 14, 25–27]. Identifying patients with progressive ILD in clinical practice is likely most effectively achieved using a multidimensional 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 a documented decline in FVC, are predictive of a worse decline in FVC in patients with fibrosing ILDs [28–30]. 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 ⩾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 has 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, in agreement 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 were 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. As an example, a subject may have been entered into Group C based on the investigator having no evidence of an FVC decline of $\geqslant$5% predicted within the prior 24 months when in fact such a decline in FVC had occurred but had not been documented. Because no data on the progression of ILD prior to subjects entering the INBUILD trial were collected, we were unable to investigate more specific subgroups than were covered by the inclusion criteria. For example, we were unable to investigate whether subjects who had a decline in FVC $\geqslant$10% predicted over the prior 24 months had a greater decline in FVC during the trial than subjects who had a decline in FVC $\geqslant$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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This study is registered at ClinicalTrials.gov (NCT02999178). To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (*e.g.* study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim policy on transparency and publication of clinical study data: https://trials.boehringer-ingelheim.com/. Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical study reports and related clinical documents can also be requested *via* https://trials.boehringer-ingelheim.com/. All requests will be governed by a document-sharing agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a data-sharing agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use https://trials.boehringer-ingelheim.com/ to request access to study data.

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